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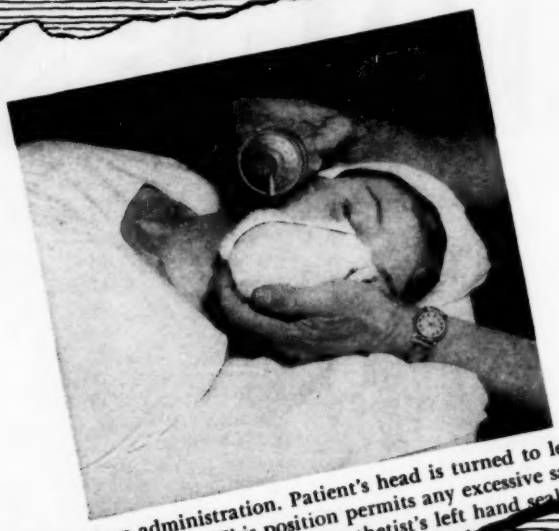

Fig. 21. Open drop administration. Patient's head is turned to left if anesthetist is right handed (or vice versa). This position permits any excessive saliva to run out of mouth rather [illegible] pool in pharynx. Anesthetist's left hand seals junction between [illegible]

A

C

B

D

Fig. 44. Immediate postoperative care. *A*, Holding up chin and feeling patient's breath. *B*, Oropharyngeal tube pulled out 2 or 3 cm., before patient emerges to stage II. *C*, Suction of trachea. A "velvet" tipped metal tube is used, the straight part being 8 inches long, and handle end offset for vision. A fairly stiff rubber, woven, or plastic catheter may be used instead. Lead plate protects teeth from injury. *D*, Postoperative position before awakening. Patient lies on arm that has [illegible] venous needle, and is held [illegible]

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THE MANAGEMENT OF ACUTE RENAL INSUFFICIENCY

Major W. H. Meroney (MC), U. S. Army
and
Lieut. R. F. Herndon (MC), ORC

Recent experience in the management of acute reversible renal insufficiency with oliguria in war casualties has allowed development of methods that should be useful in civilian practice; recommendations are accordingly offered for the management of the major problems of this condition, based on studies of 46 patients who were examined repeatedly by simultaneous clinical, chemical, and electrocardiographic techniques. These patients were all previously healthy young men who had sustained severe trauma, usually with massive blood loss and prolonged shock, and who were resuscitated with difficulty. Although large amounts of whole blood were administered, transfusion reaction was an uncommon cause for renal failure; the only factors common to most of the patients were trauma and shock. These facts should be kept in mind if the methods are applied to civilian patients whose age, physical condition, and degree of trauma are not comparable. It is not the purpose of this report to review the basic work on electrolyte metabolism nor to dwell on points of difference between previous observations and our own; rather, this report is intended to provide a brief outline of a system that was practical in the combat zone of Korea. A detailed account and discussion of the experience and basic studies will be presented separately.

Except during the first few hours after operation, a urine output of less than 20 cc. per hour in the presence of normal blood pressure and adequate fluid intake is presumptive evidence of renal insufficiency, and in this series this diagnosis was confirmed in all such patients. Other causes for oliguria, such as dehydration, were not observed. Water loading as a test for dehydration is contraindicated if renal insufficiency is present and should not be necessary for the diagnosis of dehydration. If oliguria is accompanied by hypotension, it should be assumed that the oliguria is secondary to low filtration pressure, and the diagnosis of renal insufficiency should not be attempted until normal blood pressure is restored. Renal insufficiency occurring without oliguria does not require immediate treatment, if any, and will not be discussed here. To measure the urinary output of patients with this condition accurately, it is usually necessary to use an indwelling urethral catheter, which should be irrigated twice daily with a bland fluid that is measured when instilled and recovered. In addition to its hygienic value, irrigation obviates the embarrassing sequelae of a plugged catheter. In our experience total anuria did not occur; two apparent occurrences proved to be instances of mucous obstruction of the catheter. This complication or mechanical obstruction higher in the outflow tract should be suspected if no urine whatever is obtained. The diagnostic value of an accurate record of hourly urinary output is sufficient to justify the physician's personal supervision of the details. Careful interpretation of this information may save much laboratory work and prevent the inadvertent administration of excess fluids.

The problems in management of patients with this condition will be considered in the order of urgency of action by the physician.

FLUID BALANCE

First and continuing consideration should be given to the prevention of overhydration. The evils of water intoxication are well known, yet this preventable complication is common. The total fluid intake per 24 hours should be in the range of 500 to 600 cc. plus the measured output, increasing to about 700 to 800 cc. plus the measured output if the weather is hot or the patient is feverish. The measured output usually is the total of urine and gastric suction, although diarrhea, not present in our cases, might increase the output significantly. This average intake allowed a daily weight loss of ½ to 1 lb. (0.23 to 0.5 kg.) without producing clinical evidence of edema or dehydration. The best route for administration of the fluids is oral, if the patient is able to tolerate them. In our patients, however, fluids administered orally, even by

From the 11th Evacuation Hospital, Eighth U. S. Army, Renal Insufficiency Center (Major Meroney, Chief).
Major Meroney is now with the Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D. C.
This project was carried out at the Renal Insufficiency Center, Korea, as an activity of the Surgical Research Team, Army Medical Service Graduate School, Washington, D. C. Col. F. M. Seymour and Col. R. P. Mason, Drs. A. C. Corcoran and S. M. Levenson, Capt. J. M. Howard, and the staff of the 11th Evacuation Hospital assisted in this study. The laboratory procedures reported were performed by Corp. B. F. Pease and Corp. J. T. Mackemull.
A section of this paper was presented in abstract form before the American Federation for Clinical Research, Midwestern Section, Chicago, Oct. 29, 1953.

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duodenal tube, provoked vomiting. This compounded the problems of fluid and electrolyte balance and also added the risk of aspiration pneumonia; thus the intravenous route was used almost exclusively. Restriction of orally administered fluids can be quite difficult. Patients so restricted often suffer a cruel thirst, yet their thirst is not an accurate gauge of their needs. If allowed to drink freely, they will literally drown themselves. When denied fluids they develop great craftiness in prevailing on compassionate neighbors and attendants for small sips of any fluid or for pieces of ice, a bountiful and easily overlooked source of water. When unobserved they will quaff heartily from flower vases, emesis basins, or urinals with great stealth and cunning. It is the physician's responsibility to prescribe the proper amount of water and to insure that no violation of his order occurs. Careful oral hygiene and unlimited quantities of chewing gum, together with an explanation of the reasons that compel the apparent cruelty, are usually adequate to control

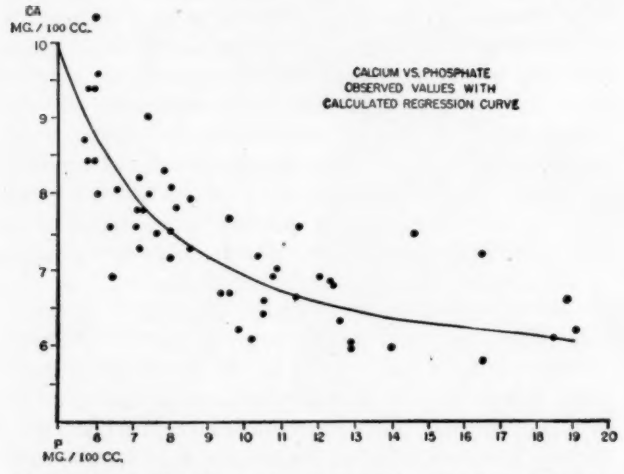

Fig. 1.—Graph of random pairs of phosphate and calcium determinations in oliguric patients.

thirst. The amount of water prescribed must contain all the solids to be administered during the 24 hours; these will be discussed later.

POTASSIUM INTOXICATION

The only chemical abnormality that is likely to cause death in the first week of uremia is potassium intoxication. Normally, potassium exists in high concentration inside cells but does not exceed a level of 5.5 mEq. per liter in the plasma. Normal daily catabolism of cells provides the plasma with a small quantity of potassium that is readily excreted. This amount of potassium can be handled by an anuric patient for many days, even several weeks, without accumulation of significant quantities in the plasma.[1] However, the basic condition that originally produced the renal insufficiency is often characterized by excessive loss of potassium from cells. This was especially evident in these patients, many of whom had suffered extensive tissue damage from trauma or infection and in whom the plasma potassium rose to high levels as early as the second day of oliguria. Devitalized tissue, whether permanently destroyed or temporarily embarrassed by trauma, infection, chemical or physical agents, or hypoxia, gives up potassium to the plasma.[2] In the plasma excess potassium is exceedingly toxic, and the first and most important evidence of toxicity is cardiac.

The toxic effect of potassium on the heart is recorded on the electrocardiogram long before any other signs or symptoms appear. The degree of electrocardiographic abnormality produced by a given excess of plasma potassium will vary widely, however, depending on the activity of other factors. Under experimental conditions, such as the infusion of potassium into the plasma of normal dogs, it has been shown that the electrocardiographic effects of progressive increments of plasma potassium are mostly consistent[3]; in clinical situations, however, the electrocardiogram has not previously been shown to be a reliable gauge of the plasma potassium level. The function of the heart with respect to potassium is the result not only of the absolute level of plasma potassium but also of factors that influence the effects of potassium. The electrocardiogram is, in fact, an accurate gauge of the plasma level of potassium in man when there is no abnormality except hyperpotassemia.[4] The discrepancies stem from the rarity with which pure hyperpotassemia occurs. In the oliguric patient substances that normally would be excreted in the urine are retained within the body, and some of these substances affect the behavior of potassium.

Calcium.—The retention of inorganic phosphate, though not itself harmful, is associated with a fall in the level of plasma calcium during oliguria. Figure 1 demonstrates the consistency with which a given excess of plasma phosphate is associated with a predictable deficit of plasma calcium. A deficit of plasma calcium is of cardinal importance during oliguria, because calcium is a specific antagonist of potassium and hyperpotassemia and hypocalcemia occur at the same time. As the plasma potassium level rises, the degree of toxicity recorded by the electrocardiogram is consistent with it only if the plasma calcium level is maintained; otherwise, the electrocardiographic abnormality and the threat to the patient's life are greatly increased. Since in oliguria the plasma calcium level regularly is depressed by a rise in the plasma phosphate level at the same time that the plasma potassium level rises, the electrocardiogram of the untreated patient bears little relationship to the plasma level of potassium. Replacement of the calcium deficit produces a striking improvement in the electrocardiogram, which then is reverted to that degree of abnormality characteristic of the plasma potassium level (fig. 2). The improvement following a single intravenous injection of calcium, however, is very transient. The plasma level of calcium falls quickly from the high level immediately after injection to the preinjection level, which is governed by the phosphate concentration. Although a rise in the plasma phosphate level reduces the plasma calcium level, the converse is not true; phosphate, unlike calcium, cannot be driven into the body repositories by such a maneuver. Intravenous dextrose infusion

1. Welt, L. G., and Peters, J. P.: Acute Renal Failure: Lower Nephron Nephrosis, Yale J. Biol. & Med. **24**: 220, 1951.
2. (*a*) Fenn, W. O.: The Role of Potassium in Physiological Processes, Physiol. Rev. **20**: 377, 1940. (*b*) Meroney, W. H.: Unpublished data.
3. Winkler, A. W.; Hoff, H. E., and Smith, P. K.: Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride, Am. J. Physiol. **124**: 478, 1938.
4. Herndon, R. F.; Meroney, W. H., and Pearson, C. M.: Unpublished data.

will cause a slight reduction in the plasma phosphate level, but not enough to allow a rise in the plasma calcium level sufficient to antagonize potassium. Short of hemodialysis, the only effective way to maintain a normal level of calcium in plasma that is high in phosphate is by continuous intravenous infusion of calcium. The effect of calcium on potassium toxicity is purely one of antagonism. The measurable level of potassium, as well as phosphate, is unaffected by raising the plasma calcium level. Once the calcium deficit is replaced, the electrocardiogram reflects the plasma level of potassium rather accurately, although still other factors, less apparent in these patients, have been shown to be influential.[5] Digitalis, which was rarely indicated in our patients, antagonizes potassium [6] in a manner similar to calcium. Digitalis and calcium appear to be additive in this respect, and great care should be used if both agents are administered to the same patient. There is particular danger if the excess potassium is suddenly removed by hemodialysis,[7] allowing digitalis, enhanced by a high calcium concentration, to exert its toxicity without the opposing action of potassium.

Small excesses of potassium produce no electrocardiographic abnormality except elevation and peaking of the T waves, best seen in the precordial leads (fig. 3). As

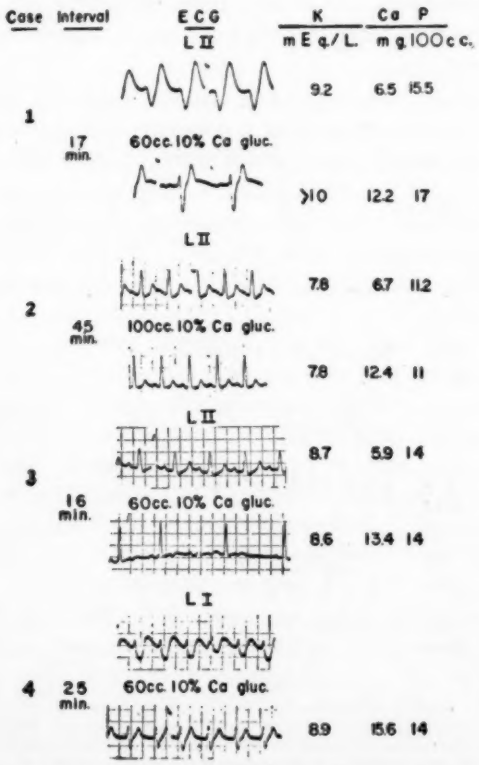

Fig. 2.—Effects on the electrocardiograms of four uremic patients with advanced potassium intoxication of intravenous infusion of calcium.

the plasma potassium level increases further, the T wave abnormalities progress in the precordial leads and become obvious in the limb leads, but they have no quantitative significance in severe hyperpotassemia. Progressive changes in the QRS complex, best seen in the limb leads, are much more ominous. In the limb leads the angle between the S wave and the ST segment widens and encroaches on the horizontal component of the ST segment until it is obliterated. P waves disappear; the T waves diminish in height and become rounded at the top; and finally, the R-S angle increases, and the smooth biphasic curves resemble a sine wave. When mild intoxication, indicated by T wave abnormality only, suddenly progresses to the severe intoxication indicated by QRS widening, it usually is the result of a fall in the plasma calcium level. Infusion of calcium should cause instant

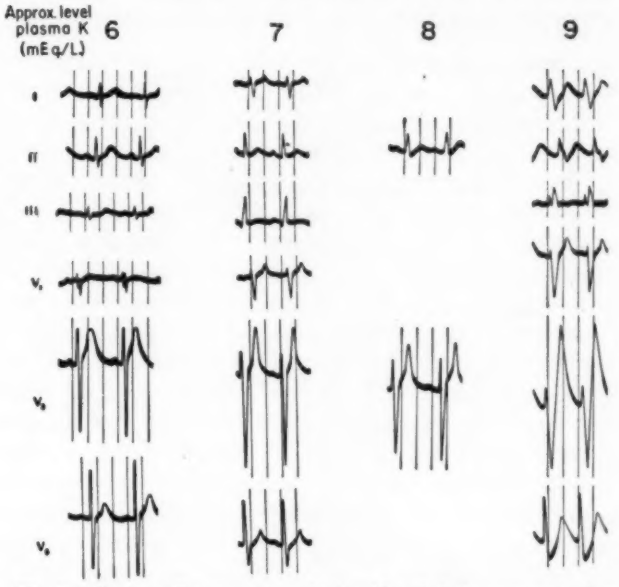

Fig. 3.—Electrocardiograms of patients with relatively pure potassium excess. Peaked T waves are seen throughout the series; when the plasma potassium level reaches 7 mEq. per liter, wide QRS complex and wide S-ST angle appear; these abnormalities increase at the level of 8 mEq. per liter, with a wide R-S angle; the final electrocardiogram shows marked deterioration and may show nodal rhythm.

reversion of the tracing to its former degree of abnormality. If calcium does not produce an immediate effect, this indicates that the plasma potassium level has increased. Sudden rises in the plasma potassium level occur during oliguria when tissue cells are subjected to stress. Hemolysis, infection, or trauma may allow the release of all the potassium contained in the affected cells. Smaller amounts of potassium may temporarily leave hypoxic cells, only to be recovered by the cells when normalcy is restored. Hypoxia from hypotension, convulsions, certain types of anesthesia, pulmonary edema, and simple breath-holding has been observed to cause such a reversible shift of potassium.[8] In our experience, a rapid increase in the electrocardiographic evidence of potassium intoxication that was not responsive to calcium invariably was associated with a rapid increase of the plasma potassium level associated with one of the above

5. (*a*) Darrow, D. C.: Medical Progress; Body-Fluid Physiology: The Role of Potassium in Clinical Disturbances of Body Water and Electrolytes (part 1) New England J. Med. **242**: 978, 1950; (part 2), ibid. **242**: 1014, 1950. (*b*) Abrams, W. B.; Lewis, D. W., and Bellet, S.: The Effects of Acidosis and Alkalosis on the Plasma Potassium Concentration and the Electrocardiogram of Normal and Potassium Depleted Dogs, Am. J. M. Sc. **222**: 506, 1951. (*c*) Keating, R. E., and others: The Movement of Potassium During Experimental Acidosis and Alkalosis in the Nephrectomized Dog, Surg., Gynec. & Obst. **96**: 323, 1953. Fenn.[2a]

6. Hopper, J., Jr.; O'Connell, B. P., and Fluss, H. R.: Serum Potassium Patterns in Anuria and Oliguria, Ann. Int. Med. **38**: 935, 1953.

7. Lown, B., and others: Effects of Alterations of Body Potassium on Digitalis Toxicity, read before the American Society for Clinical Investigation, Atlantic City, N. J., May 5, 1952, abstracted, J. Clin. Invest. **31**: 648, 1952. Meroney.[3b]

8. Stewart, J. D.; Potter, W. H.; Hubbard, R. S., and Andersen, M. N.: Potassium Movement in Acute Liver Damage, Ann. Surg. **138**: 593, 1953. Fenn.[2a] Meroney.[3b]

conditions. Progressive potassium intoxication caused no symptoms in these patients until it had reached the stage at which the electrocardiogram showed severe deterioration similar to that of the fourth tracing in figure 3. Patients who had symptoms with a less abnormal electrocardiogram were found to have other causes for their symptoms. Many of the disorders associated with hyperpotassemia, such as those noted above, produce severe symptoms. Correction of the basic condition relieved the

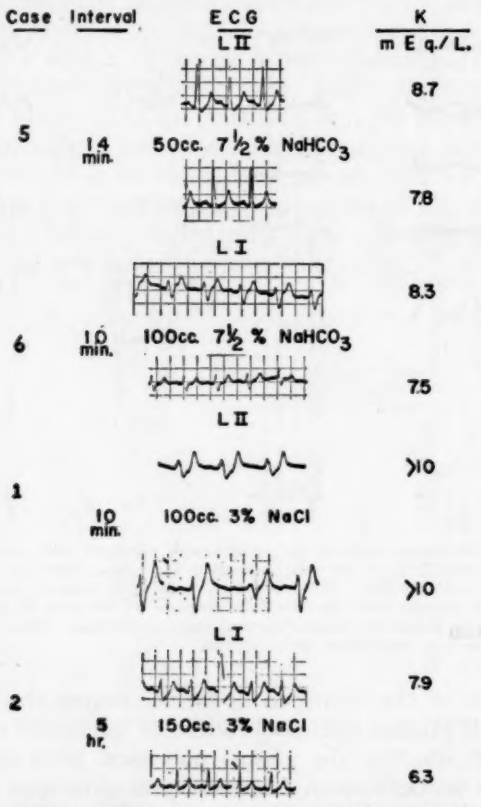

Fig. 4.—Electrocardiographic effects of the administration of sodium bicarbonate and sodium chloride to patients with potassium intoxication.

symptoms in our patients, although in many instances the plasma potassium was still greater than 8 mEq. per liter and the electrocardiogram was appropriately abnormal. At the time of the tracings shown for case 1 in figure 2, the patient had neither signs nor symptoms. If one attempts to follow the course of the intoxication in patients with this condition by changes in tendon reflexes, respiratory symptoms, or any other known means except electrocardiography or blood chemistry, the patient will probably be dead before corrective action can be taken.

Sodium.—Another ion that should be used in the practical management of potassium intoxication is sodium. Sodium and potassium are inversely related in the plasma of the oliguric patient; raising the plasma sodium concentration causes a fall in plasma potassium concentration and modifies the electrocardiographic effects of potassium intoxication (fig. 4). Potassium concentration is depressed with a rise in sodium concentration independently of the other ions involved, indicating that the agent responsible for the change is sodium and not the anion. An akaline salt of sodium is preferred, however, because the retention of organic acids regularly produces acidosis in these patients. The changes in the concentration of potassium and the other substances are not attributable to dilution. Although tissue analyses were not performed, it is presumed that raising the plasma sodium concentration forces potassium back into cells. The improvement in the electrocardiogram that followed a rise in the plasma sodium level and a fall in the plasma potassium level was sometimes greater than would be expected from the lower level of potassium. This suggests that sodium, in addition to depressing the plasma concentration of potassium, may also have some antagonistic effect similar to that of calcium. Figure 5 shows the beneficial effect of raising the plasma calcium level followed by still further improvement from administration of sodium chloride. The last tracing in this series is almost normal, although the potassium concentration still is 7.2 mEq. per liter. Obviously, all of the factors influencing the response of the electrocardiogram to a given potassium concentration have not been considered. Infusions of hypertonic solutions of sodium salts do, however, provide an effective and practical means for modifying potassium intoxication. Again it is emphasized that all of the patients in this series were young men without known previous cardiovascular disease, a fact that undoubtedly influenced their responses and that should be considered if these methods are applied to dissimilar patients.

Dextrose.—The plasma potassium level may also be reduced by the infusion of a hypertonic dextrose solution.[9] Its metabolism, which can be hastened with

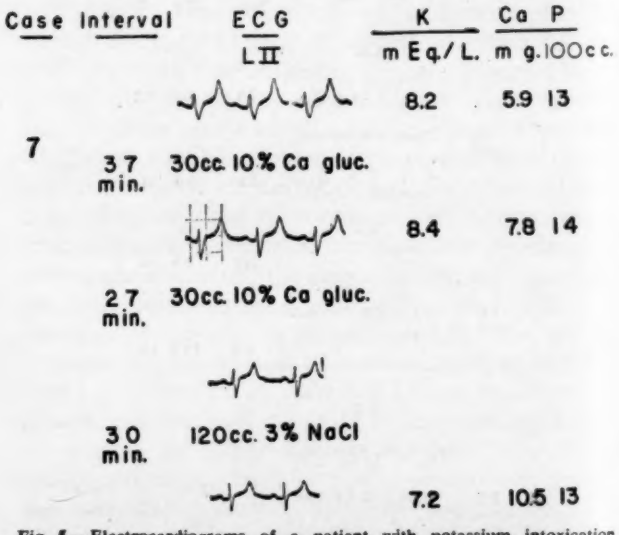

Fig. 5.—Electrocardiograms of a patient with potassium intoxication showing improvement following two elevations of the plasma calcium level and further improvement from subsequent administration of sodium chloride.

exogenous insulin, removes potassium and phosphate from the plasma. While calcium antagonizes the effects of potassium without changing the quantity present in the plasma and sodium forces potassium into cells by some physicochemical means, glucose carries potassium into cells by a more active process. As glycogen is formed, potassium, as well as phosphate, is incorporated into the carbohydrate complex; this is an effective, though slow, method of controlling potassium intoxication. Results

9. Fenn, W. O.: Deposition of Potassium and Phosphate with Glycogen in Rat Livers, J. Biol. Chem. **128**: 297, 1939. Fenn.[2a] Darrow.[5a]

similar to those of a dextrose-insulin combination could be expected from the use of fructose, which does not require insulin for its early metabolism, but this compound was not used. If dextrose is to be used effectively by the intravenous route, it should be given continuously. Intermittent intravenous injection of dextrose causes a sharp spike in blood sugar level followed by hypoglycemia. The hypoglycemic period has the double disadvantage of failure to remove potassium during that period and provocation of glycolysis with further release of potassium to the plasma. Also, if nutrition is limited to intermittent intravenous feedings of dextrose, the period between infusions is one of relative starvation, which is characterized by cell destruction and release of potassium.

On the basis of the above observations the following standard solution was devised and was found to be effective in controlling potassium intoxication for many days.

Calcium gluconate 10%.....100 cc.
Sodium bicarbonate 7.5%..... 50 cc.
Dextrose 25% in H_2O.....400 cc.
(Containing 50 units of regular insulin)
Isotonic sodium chloride solution or
1/6 M sodium lactate.....Volume of output

This solution should be given intravenously, preferably through a catheter, in a large vein at a constant rate of about 25 cc. an hour. Water-soluble vitamins should be added to this basic solution. Our patients received daily 2 gm. of ascorbic acid, 50 mg. of thiamine chloride, and 20 mg. of vitamin K, but this vitamin prescription was chosen in the interests of a concurrent study of wound healing and is not necessarily optimal. If the laboratory can provide frequent determinations of plasma sodium levels, the sodium content of the fluid should be varied to maintain a plasma level of about 150 mEq. per liter. If not, the amount suggested can be given empirically without fear. The only complication arising from administration of more than the desired concentration is aggravation of thirst. This is uncomfortable for the patient, and if he is allowed excess water pulmonary edema may be provoked. None of the dire effects attributed to sodium administration [10] were observed in these patients, and it would appear that it is not the sodium alone but the excess water that may accompany it that is dangerous. In older patients or in those who have cardiovascular disease, additional hazards may be associated with a high plasma sodium level. It is unlikely, however, that the dosage recommended would have adverse effects. A likelier source of harm is overhydration; the necessity for water restriction must be kept constantly in mind. If frequent determinations of the plasma potassium level show that it is not elevated, it would not be necessary to use calcium in the infusion, as its purpose is to antagonize an elevated plasma potassium level. The only other reason for giving calcium would be to prevent tetany if the plasma calcium level were depressed. However, in patients with this condition the plasma calcium level is not depressed unless the potassium level is elevated, because hypocalcemia is caused by an elevation of the plasma phosphate level, and phosphate rises at the same time as potassium; therefore, calcium should be given only if the plasma potassium level is elevated. If frequent determinations of potassium cannot be done, the electrocardiographic changes noted are sufficiently specific to guide logical therapy. The constituents of the basic solution should be tailored for the individual patient when possible. If an item is omitted, its volume should be replaced by an isotonic solution or distilled water.

Ion-Exchange Resins.—Ion-exchange resins are effective agents for the withdrawal of potassium from the plasma into the intestine under certain circumstances.[11] In this series of patients, however, those whose potassium levels were highest were unable to take anything by mouth. Rectal instillation of resins was attempted repeatedly, but such intractable concretions were formed that the amount of water necessary to remove them caused water absorption and overhydration. An attempt was made to contain resins in a silk tube that could be inserted and extracted from the rectum mechanically, but the procedure was very painful for the patient; effective exchange occurred only at the surface of the resin bolus, even when a silk tube of only 5 mm. diameter was used; and only 7 mEq. of potassium was extracted by 30 gm. of resin left in the rectum for 24 hours. It was intended to utilize a colostomy for this method but a suitable patient was not found. The impression was gained that resins would not be more effective than the intravenous therapy described.

Dialysis.—Artificial-kidney dialysis is the most effective treatment known for removing potassium, but dialysis for hyperpotassemia alone is, in our experience, rarely indicated. The use of this technique is discussed below under the heading Clinical Uremia. We have had no experience with other methods of dialysis.

LESS URGENT PROBLEMS IN MANAGEMENT

Nutrition.—Principally fat and carbohydrate are recommended during the oliguric phase of acute uremia, because of the potential toxicity of protein.[12] Maximal caloric intake is desirable to prevent the patient from burning his own tissues to supply his caloric needs, but the exact quantity of fat or carbohydrate necessary is unknown. Various high calory mixtures, such as olive oil and glucose, frozen butter balls, and commercial fat emulsion preparations were given by mouth and by gastric and duodenal tube. Unfortunately, the patients who needed it most were nauseated by any of the forms of oral feeding. Intravenous administration of fat was not done in these patients because a satisfactory preparation was not available.[13] Caloric intake, in the main, was limited to intravenous administration of dextrose, which was given as outlined above. This is far from ideal but

10. Swann, R. C., and Merrill, J. P.: The Clinical Course of Acute Renal Failure, Medicine **32**: 215, 1953.

11. Elkinton, J. R., and others: Treatment of Potassium Retention in Anuria with Cation Exchange Resin, Am. J. M. Sc. **220**: 547, 1950. Danowski, T. S., and others: The Use of Cation Exchange Resins in Clinical Situations, Ann. Int. Med. **35**: 529, 1951.

12. Kolff, W. J.: Forced High-Calorie, Low-Protein Diet and the Treatment of Uremia, Am. J. Med. **12**: 667, 1952. Welt and Peters.[1]

13. Creditor, M. C.: Some Observations of Effects of Intravenous Fat Emulsions on Erythrocyte Fragility, Proc. Soc. Exper. Biol. & Med. **82**: 83, 1953.

will sustain the patient. Current studies with newer antiemetic drugs offer hope for successful oral or tube feeding.

Clinical Uremia.—After a few days of oliguria (in this series five to eight days), the syndrome of clinical uremia develops. The patient gradually becomes lethargic and shows evidence of mental torpor, yet his extremities are tremulous and hyperreflexic. The nausea that may have been present for days now becomes active vomiting and retching. Intractable hiccups are usual. These clinical manifestations first appeared in our patients when the plasma nonprotein nitrogen level was about 250 mg. per 100 cc. The consistency with which this figure was associated with the clinical findings was remarkable, and it came to be useful in allowing one to predict from a nonprotein nitrogen value of about 200 mg. per 100 cc. that the patient would show the symptoms of uremia on the following day. At this juncture artificial-kidney dialysis is strongly indicated. Six hours of dialysis will produce dramatic relief of symptoms as well as restoration of electrolyte balance. It does nothing for renal function, of course, but it clears the plasma of the substances that normally would have been excreted in the urine. The patient is then ready to start anew on his course of uremia; if diuresis does not occur within several days, dialysis should be repeated each time the symptoms recur until renal function is recovered. Dialysis was performed one or more times in 27 of our 46 patients; 14 underwent dialysis once, 6 twice, and 7 three times.

It is important to recognize the syndrome of clinical uremia and to know when to expect it, because similar signs and symptoms can be produced by hypotension or sepsis. In our patients with renal insufficiency the nonprotein nitrogen rose gradually to the critical level of 250 mg. per 100 cc. over a period of about a week. This level or symptoms of uremia did not occur before the fifth day of oliguria, and the average was later. When symptoms appeared dialysis usually was performed, eliminating the symptoms. If dialysis was not performed the symptoms progressed gradually, and two or three days elapsed before such threatening clinical manifestations as coma, convulsions, and pericarditis appeared. In patients with prerenal azotemia secondary to shock or sepsis, symptoms appeared at any time, usually within one or two days, and were totally unrelated to the nonprotein nitrogen level. The onset often was abrupt and the progression rapid. Dialysis was quite successful in restoring chemical balance but did not improve the clinical manifestations. The rate at which plasma potassium and phosphate levels rose after dialysis also was quite different from that seen in patients with renal insufficiency. Within a day, or even a few hours, of a normal postdialysis level, great increments of potassium and phosphate were again found in the plasma. The condition that had produced the symptoms was still present, and it was associated with devitalization of tissue, which gave up its intracellular materials to the plasma. Dialysis, therefore, was virtually useless, and time was lost in this procedure that should have been spent in treating the basic condition of the patient.

The measures outlined for the treatment of potassium intoxication were effective, in patients without necrotic tissue, for the period prior to the appearance of clinical uremia. In some instances dialysis was avoided because diuresis occurred before clinical uremia appeared, and in others, the use of these measures made fewer dialyses necessary. In the presence of clinical uremia no attempt was made to control potassium further by medical means, because the dialysis that was otherwise indicated was superbly effective in removing potassium. When an artificial kidney is not available, medical management of potassium intoxication may save the patient's life for the moment but should be used with a view to providing time for transport to a renal center. Where an artificial kidney is available, this method will allow dialyses to be performed on a reasonable schedule for clinical uremia only and should obviate emergency dialyses for potassium intoxication.

Anemia and Hemorrhage.—Of the various causes of anemia in post-traumatic renal insufficiency, the only one studied in this series of patients was severe purpura similar to that seen in chronic uremia. Bleeding into the skin, nasopharynx, and intestine appeared after 12 to 15 days and was related only to the duration, not the severity, of the uremia. Unlike the other manifestations of uremia, the hemorrhagic tendency was entirely unaffected by artificial kidney dialysis or by diuresis; to the contrary, the severest bleeding occurred several days after the onset of diuresis. The only positive temporal relationship was the cessation of bleeding with the resumption of normal diet; however, the absence of hemorrhagic diathesis during pure starvation discourages speculation on this point.

A search for the cause of the bleeding revealed no intrinsic clotting defect, only capillary fragility. The condition was unrelated to abnormality of plasma electrolytes and was unaffected by vitamins C or K or fresh blood transfusions. The replacement of the blood lost was considered desirable, yet transfusions were feared because a minor reaction might have exaggerated significance in patients so seriously ill. Nevertheless, small transfusions, 200 to 300 cc. daily, were given regularly without apparent harmful effect. Bleeding was originally considered a contraindication to artificial kidney dialysis, because of the necessity for heparinization before and during the procedure. On several occasions, however, dialysis was performed as a lifesaving procedure on patients who were bleeding. During the procedure large quantities of blood were available for immediate use if bleeding should be aggravated, and after the neutralization of heparin with protamine at the end of the procedure, packed erythrocytes were given. No alarming bleeding occurred, and so it became the practice to perform dialysis whenever indicated, regardless of hemorrhagic tendencies. The risk of dialysis in the presence of hemorrhage was considered to be less than the risk of the complications of uremia if dialysis were withheld, and subsequent experience supported this view.

Infection and Antibiotics.—The specific infections encountered in battle wounds in these patients will not be reviewed here. In general, their successful management depended mainly on thorough and frequent dressings. An amount of devitalized tissue and infection that may be acceptable in a patient with normal renal function may be lethal in the oliguric patient. Small amounts of tissue, particularly muscle, contain sufficient potassium to kill if it is released into plasma that is not being cleared by the kidney. Removal of such tissue must be prompt and thorough, and the approach must be much more radical than is customary with good surgeons. If the point at which devitalized tissue merges with normal tissue is not apparent to the surgeon, he should débride farther. Excessive débridement may cost the patient precious tissue, but inadequate débridement may cost his life. Remnants of devitalized tissue usually can be suspected if the plasma potassium and phosphate levels are inordinately high with respect to nonprotein nitrogen. The measures outlined above will control the potassium level; the phosphate level, however, is little affected by such measures, and it is a useful index of the presence of necrosis. A plasma phosphate level reaching 10 mg. per 100 cc. before the nonprotein nitrogen level reached 150 mg. per 100 cc. indicated severe tissue destruction in these patients, and on several occasions deep necrosis underlying a wound with a clean surface was first suspected from this relationship. Antibiotics cannot be relied upon to control infection in devitalized tissue. Also, the proper methods for administration of antibiotics have not been clarified. The principal route for excretion of antibiotics is through the urine, and during oliguria tremendous concentrations accumulate in the blood if usual doses are given. The importance of this fact was not investigated in these patients, but recent reports of serious intoxication from certain antibiotics require that great caution be observed.[14]

The systemic infection oftenest seen in patients with this condition is pneumonia. This complication is particularly likely to occur if the syndrome of clinical uremia is present and is not interrupted by hemodialysis. The hazard of pneumonia was combated in these patients by deep breathing exercises, voluntary coughing, frequent turning, and good general nursing care. Patients whose cooperation was doubtful because of associated wounds or illnesses were placed on Stryker frames so that turning and drainage could be assured. The diagnosis of oliguria carries with it a poor prognosis, although the renal lesion itself is usually reversible. The onset of infection may well be enough additional insult to cause a death that would not otherwise have occurred. The seriousness and the potential reversibility of the illness demand that no effort be spared in preventing or treating the complication of infection.

Salt Wasting During Diuresis.—The onset of diuresis was arbitrarily defined in these patients as the day on which urine volume exceeded one liter. Once this volume was reached, the output increased rapidly, often 100% or more on successive days, until a peak volume of 3 to 6 liters was attained. As the urine volume increased, the urinary concentration of nonprotein nitrogen, sodium, potassium, and phosphate increased similarly, and the total output of salts reached high values within one or two days. At this stage the kidneys excrete salts wantonly, without regard for the body's needs. Fortunately, appetite and food tolerance have returned at this stage, and salt depletion is partially offset by the food intake. Daily supplements of sodium and potassium, however, must be added to prevent serious depletion. Sodium chloride, 4 to 6 gm., and potassium chloride, 1 to 2 gm., added to a regular diet daily for about a week were found to be adequate. Fluids were administered freely without noticeable aberrations of fluid balance.

SUMMARY

In a study of acute renal insufficiency in war casualties, it was found that total fluid intake per 24 hours should vary between 500 and 800 cc. plus the output. Potassium intoxication, the only chemical abnormality that threatens the patient's life during the first week of oliguria, produces no clinical signs or symptoms in patients with this condition until death is imminent. The electrocardiogram shows early and continuing evidence of the intoxication, and if other plasma chemicals are at normal levels the electrocardiogram is a rather accurate gauge of the plasma potassium concentration. Plasma calcium is depressed, however, when potassium is elevated, because of the associated retention of inorganic phosphate. As calcium is a specific antagonist of potassium, its administration causes striking modification of the electrocardiographic effects of potassium intoxication. Administration of sodium or of dextrose with insulin lowers the plasma potassium level. Continuous infusion of a standard mixture of calcium, sodium, and dextrose will protect the patient from potassium intoxication for many days, allowing transportation of the patient to a center where hemodialysis can be performed if necessary.

14. Bateman, J. C., and others: Fatal Complications of Intensive Antibiotic Therapy in Patients with Neoplastic Disease, A M. A. Arch. Int. Med. **90**: 763 (Dec.) 1952.

Increase in Population.—World population now appears to be growing at the unprecedented rate of slightly more than one percent per year. Some 25 million people were added in 1953. That is at the rate of about 70,000 daily. If the present growth rate persists, numbers would exceed 3.5 billion by 1980, an increase of 46 per cent above the 1950 total. By the year 2000, approximately 4.1 billion people would inhabit the earth; by 2050, about 7 billion. . . . There was a very slow increase until 1650. . . . About a fourth of all Europeans died in 1347-1349, the years of the Black Death. Between 1200 and 1600, England averaged seven famines each century, and these resulted in a wave-like rise and fall in numbers, with no marked upward trend. Since 1650, the pattern of world population growth has changed drastically, bringing a persistent accelerating increase in the rate of growth and in total numbers. It has been estimated that between 1650 and 1850 numbers grew at an average annual rate of 0.4 per cent, at 0.7 per cent between 1850 and 1900; and at 0.9 per cent between 1900 and 1950. Now the rate of increase is over one per cent. . . . The greatly accelerated growth in the nineteenth century reflects the impacts of man's control of his environment. Jenner's smallpox vaccine in 1798 opened the way for Koch, Reed, Pasteur, and other pioneers in disease control.—World Population Round-Up, *Population Bulletin*, January, 1954.

CLINICAL RESPONSE OF SPONTANEOUS HYPOGLYCEMIA TO DIETARY AND DRUG THERAPY

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It is generally conceded that in spontaneous hypoglycemia of islet cell origin a surgical attack on the pancreas, designed to remove the hyperfunctioning incretory tumor, remains the therapy of choice. However, the need for accurate medical management is of great importance during the preoperative period, and it becomes of paramount importance when prolonged medical therapy is necessitated by the rejection of a definitive operation by the patient or when the surgical risk is believed too great. Moreover, the progressive systemic effects of functioning metastatic islet cells lying beyond the scope of ablative surgery may provoke even a greater challenge to the physician despite an ultimate grave prognosis.

Three cases of insulinoma (insulin-secreting islet cell adenoma) are reviewed. Although each patient was ultimately treated by surgery,[1] experimental observations were made during the preoperative and interim hospital course on the clinical response to dietary, alloxan, corticotropin (ACTH), and cortisone therapy. It is hoped that these data may provide useful information for formulating an approach to the medical management of spontaneous hypoglycemia, particularly in cases in which definitive surgery may be contraindicated.

More than 400 cases of spontaneous hypoglycemia due to insulin-secreting tumors have been reported to date.[2] The disease may occur at any age, having been reported in a newborn infant on whom an exploratory operation was done on the 14th day of life and also in a 69-year-old patient. The peak incidence occurs between the fourth and fifth decades with equal distribution between the sexes.

CLINICAL DIAGNOSIS

A diagnosis of an insulin-secreting tumor is tenable when the clinical symptom complex conforms with the criteria set forth in Whipple's triad; these are (1) signs and symptoms of insulin shock usually progressive, frequently induced by fasting or exercise; (2) repeated fasting blood sugar concentrations below 50 mg. per 100 cc.; (3) symptomatic relief caused by glucose administration. The commonest clinical signs and symptoms seen in 193 patients with insulinoma are listed below in a tabulation adapted from Crain.[3] The per cent of cases in which the symptom appeared is listed also. The frequency of central nervous system manifestations tends to mask the diagnosis of this pancreatic disease. Furthermore, the diagnosis is complicated by the knowledge that spontaneous hypoglycemia may be precipitated by other causes, which have been grouped into two categories and are listed in the outline below, which is modified from Conn.[4]

Loss of consciousness	58	Noisy behavior	20
Confusional state	54	Headache	20
Weakness and fatigue	41	Tremor	18
Deep coma	40	Hunger	14
Sweating	36	Babinski sign elicited	13
Drowsiness and stupor	35	Paresthesias	13
Lightheadedness	30	Irritability	11
Visual disturbances	30	Transient hemiplegia	10
Amnesia	28	Abdominal pain	8
Clonic convulsions	24	Palpitation	3

I. Organic
- A. Hyperinsulinism
  1. Pancreatic islet cell adenoma
  2. Pancreatic islet cell carcinoma
  3. Diffuse hyperplasia of islet cells
- B. Hepatic disease
  1. Infectious cholangiolitis
  2. Toxic hepatitis
  3. Diffuse hepatitis
  4. Fatty degeneration or metamorphosis
  5. Glycogenosis (von Gierke's disease)
- C. Pituitary hypofunction (anterior lobe)
  1. Destructive lesion (chromophobe tumor, cyst)
  2. Atrophy and degeneration (Simmond's disease)
  3. Thyroid hypofunction secondary to pituitary hypofunction
- D. Adrenocortical hypofunction (Addison's disease)
  1. Idiopathic cortical atrophy
  2. Destructive infectious granulomata
  3. Destructive neoplasm
- E. Central nervous system lesions (hypothalamus), interference with nervous control of blood sugar

II. Functional hypoglycemia
- A. Increased secretion of insulin by normal islet cells (possibly autonomic imbalance)
- B. Alimentary hypoglycemia
  1. Postgastrectomy (dumping syndrome)
  2. Postgastroenterostomy
- C. Renal glycosuria
- D. Lactation
- E. Severe, continuous muscular work
- F. Postoperative hypoglycemia
- G. Severe inanition
- H. Factitious hypoglycemia (surreptitious insulin administration)
- I. Unknown

The causes of 80 to 90% of all cases of spontaneous hypoglycemia are shown. Prior to definitive pancreatic surgery not only should the triad of Whipple be noted but also the other causes of spontaneous hypoglycemia

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1. dePeyster, F. A., and Gilchrist, R. K.: Surgical Aspects of Spontaneous Hypoglycemia Due to Occult Insulinoma, A. M. A. Arch Surg. **67**: 330-340 (Sept.) 1953.

2. Howard, J. M.; Moss, N. H., and Rhoads, J. E.: Collective Review: Hyperinsulinism and Islet Cell Tumors of Pancreas with 398 Recorded Tumors, Surg., Gynec. & Obst. **90**: 417-455 (May) 1950.

3. Crain, E. L., Jr., and Thorn, G. W.: Funetioning Pancreatic Islet Cell Adenomas: Review of Literature and Presentation of 2 New Differential Tests, Medicine **28**: 427-447 (Dec.) 1949.

4. Conn, J. W.: Diagnosis and Management of Spontaneous Hypoglycemia, J. A. M. A. **134**: 130-138 (May 10) 1947.

should be eliminated. Central nervous system, hepatic, renal, alimentary, lactational, and work hypoglycemias may be excluded by history or routine laboratory tests. To more clearly define spontaneous hypoglycemia due to an insulin-secreting adenoma, R. M. Wilder added a fourth requirement to Whipple's triad, namely, normal health and evidence of stability of the autonomic nervous system must have existed prior to the first episode of hypoglycemia.

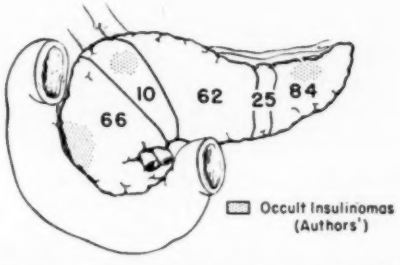

Fig. 1.—Distribution of pancreatic insulin-secreting adenomas. The numbers indicate tumors seen in the various arbitrary divisions of the pancreas. The location of the tumors seen in the cases reported on are shown. The illustration is modified from Howard.[2]

LABORATORY DIAGNOSIS

There is no specific diagnostic test to determine the presence of an insulin-secreting adenoma. A fasting blood sugar level with repeated readings of 50 mg. per 100 cc. or less is the most significant laboratory finding. Values of 40 mg. per 100 cc. or less will be observed in about 80% of patients with insulinoma. However, blood sugar level alone is not a positive criteria for diagnosis. There are instances in which blood sugar levels of 64 mg. per 100 cc. and higher are often found in prolonged coma after insulin therapy for schizophrenia.

The character of the glucose tolerance curve in spontaneous hypogylcemia due to insulinoma is inconstant, varying from a flat to a diabetic configuration. Six-hour glucose tolerance tests would appear to offer more accurate information than the shorter four-hour tests. The few insulin tolerance tests reported demonstrate a great variation of response suggesting no characteristic pattern. The subcutaneous epinephrine test for pituitary-adrenal-cortical insufficiency and the four hour corticotropin test manifest by the eosinopenic response are valuable in appraising the functional status of the adenohypophysial adrenal-cortical axis.[3] Electroencephalographic tracings on patients with insulinomas have not been diagnostic; however, high voltage, slow activity in the fasting state or with hyperventilation have frequently been observed. Administration of glucose may provoke a return to normal.

PATHOLOGY

Benign or malignant insulinomas show a wide range of variability as to size, multiplicity, and location in and about the pancreas (fig. 1). An incidence of 5 to 10% of malignant growths has been encountered varying from capsular invasion to distant metastasis. The tumor may measure from 1 mm. to 15 cm. in diameter. The tumor appears grossly on cut section to be firm, homogenous, and often demarcated from the surrounding tissue by a thin capsule of condensed fibrous tissue (fig. 2). Microscopically, a wide range of cells resembling those of pancreatic beta cell tissue is encountered, arranged in rosette, medullary, or trabecular patterns (fig. 3). Sparse or diffuse stroma may be present. Lopez-Kruger and Dockerty have published an excellent review of the pathology of tumors of the islands of Langerhans.[5]

An inconstant correlation of hyperinsulinism activity with the histological pattern is observed. Specific beta granules usually associated with insulin formation in normal islands are not always found in insulin-secreting adenomas, and often the granules may appear atypical. A more accurate indication of functional activity may be obtained by biological assay of insulin content. High values (7 to 100 units per gram of tissue) may be found in insulin-secreting tumors, while normal pancreatic tissue contains 2 to 3 units per gram of tissue.

THERAPY

Surgical exploration and excision of the insulin-secreting tumors is the treatment of choice. Exploration should be carried out for the following reasons: 1. Five to 10% of the tumors encountered may be malignant. 2. Irreversible central nervous system damage may result from repeated progressive uncontrolled hypogylcemia. 3. Deleterious effects of reactive sympathetic discharge in patients with low myocardial reserve are a constant hazard. 4. Spontaneous hypoglycemia must be regarded as a progressive disease that may terminate fatally within six months from onset.

Dietary Management.—Intravenous administration of 30 to 50% dextrose solution is the most effective agent for the emergency treatment of hypoglycemic coma. In

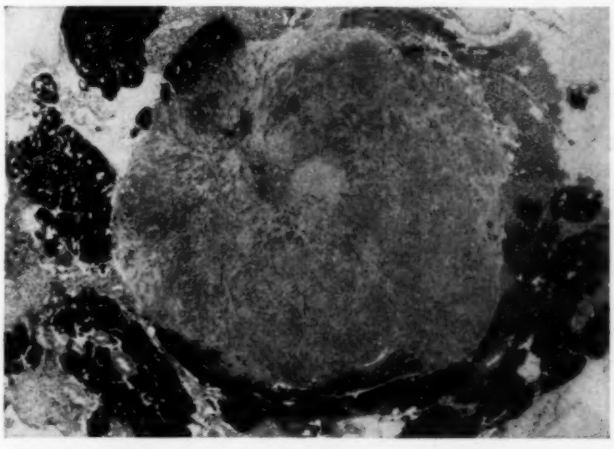

Fig. 2.—Photomicrograph showing discrete pseudoencapsulated insulin-secreting adenoma surrounded by compressed normal pancreatic tissue (case 1). Hematoxylin and eosin stain: × 7.

cases of prolonged coma resulting from hypoglycemia such as observed during insulin therapy for schizophrenia, occasionally massive intravenous dextrose injections may produce little resuscitative effect; however, if 5 to 10 units of insulin are administered, rapid recovery may take place. Oral administration of 200 cc. of milk, orange juice, or sweetened liquid will abort an impending hypoglycemic attack. Administration of glucose by proctoclysis is not reliable, because absorption is slow and incomplete.

5. Lopez-Kruger, R., and Dockerty, M. B.: Tumors of Islets of Langerhans, Surg., Gynec. & Obst. 85: 495-511 (Oct.) 1947.

In the nonemergency phase of the disease, successful medical management is predicated on the maintenance of a constant relative hyperglycemia. Unless a body weight change is desired as a part of the treatment, a diet of adequate calories (30 Cal./kg.) consisting of a high protein, variable fat, and low carbohydrate content has proved satisfactory. Such a diet should be administered in regulated frequent feedings. Because glucose is liberated into the blood stream slowly as a result of protein breakdown, a high protein diet causes a slow rise in blood sugar and thus reduces the undesired secondary hypoglycemia resulting from reactive insulin stimulation. A second advantage of a high protein diet is the fact that it provides a source of glucose that may be metabolized over a prolonged period. The use of a high fat, low carbohydrate, and isocaloric protein diet embraces some of the above advantages, but the constant threat of obesity resulting from high caloric intake must be constantly borne in mind. The frequency of feedings is perhaps more important than the composition of the diet in maintaining a relatively constant hyperglycemia. Three main meals

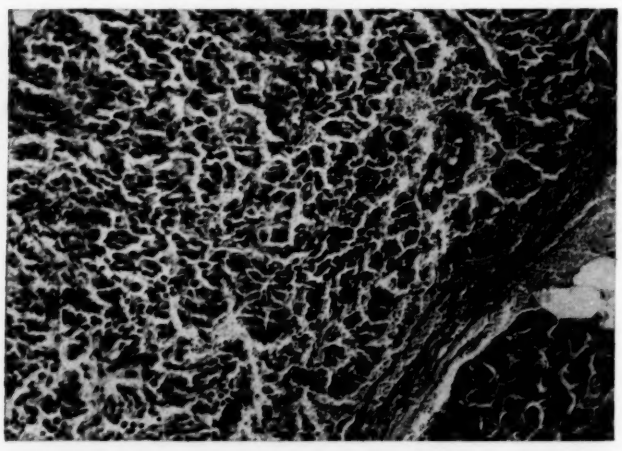

Fig. 3.—Photomicrograph of an insulin-secreting tumor showing islet cells arranged in a rosette pattern. A section of normal pancreas appears in the lower right hand corner. Hematoxylin and eosin stain: × 102.

of a balanced protein, carbohydrate, and fat content together with in-between feedings have proved effective in preventing hypoglycemic attacks. The successful dietary control of spontaneous hypoglycemia caused by an islet cell tumor is illustrated in case 1 below.

Alloxan Therapy.—Alloxan, a ureide of mesoxalic acid, when injected intravenously has a specific pancreatic beta cell necrosing action producing glycosuria in experimental animals. It has been administered with varying results in selected human patients with benign and malignant insulinoma as a chemotherapeutic effort to destroy the islet cell neoplasm. While one apparent successful therapeutic result was observed,[6] the majority of investigators report only transient symptomatic relief or therapeutic failure.[7] Adverse parenchymatous changes of the heart, liver, thyroid gland, and kidney tubules resulting from alloxan toxicity would also militate against its use. Some value occasionally might be obtained by using this drug in confirmed inoperable cases of metastatic malignant insulinoma. The experimental use of alloxan in a patient with spontaneous hypoglycemia of islet cell origin is illustrated in case 2 below.

Corticotropin and Cortisone Therapy.—The temporary diabetic response to corticotropin and cortisone is the basis for therapy in hypoglycemia caused by insulinoma. These hormones have been administered with varying results. Corticotropin and cortisone may favorably affect the course of spontaneous hypoglycemia caused by a benign or malignant pancreatic insulin-secreting tumor.[8] The effective dose of corticotropin varies from 10 mg. per day to more than 450 mg. per day. The effect of corticotropin and cortisone on spontaneous hypoglycemia is illustrated in case 3.

REPORT OF CASES

CASE 1.—A 63-year-old white dairy farmer experienced increasing nervousness six months prior to admission. This symptom was associated with daily diplopia lasting 10 to 15 minutes and followed by periods of weakness. Two months before admission, his nervousness became intensified followed by weakness terminating in coma. On being aroused, and after taking food, recovery was complete. Ten days before admission, daily attacks of nervousness and weakness occurred ending in unconsciousness for periods lasting to two hours. These attacks took place always in the morning or when the patient missed a meal.

Physical examination showed a well-developed, moderately obese white man who was well oriented and appeared in no distress. His height was 5 ft. 7 in., his weight 160 lb. (73 kg.), his pulse 68 beats per minute, temperature 98.6 F, and respiration 24. The general and neurological examinations were within normal limits. The blood cell count, urinalysis, and serologic study showed normal results. Fasting blood sugar values ranged from 26 mg. per 100 cc. to 33 mg. per 100 cc. Three glucose tolerance tests determined hourly in milligrams per 100 cc. were: 70, 110, 110, 70, 70, and 70; 40, 100, 110, 190, 90, and 40; 90, 100, 107, 110, 80, 60, and 100. Skull roentgenograms were normal. The basal metabolic rate was –1 and 0% in two tests.

A hypoglycemic attack (blood sugar 25 mg. per 100 cc.) was observed after admission during which time the patient was violent and irrational. The administration of 200 cc. of orange juice sweetened with 50 gm. of glucose relieved his symptoms. The patient was placed on a 1,941 calory diet (protein 99 gm., carbohydrate 146 gm., and fat 107 gm.) yielding 27 Cal./kg. served in three main meals at 6 a. m., 12 noon, and 6 p. m. In-between feedings were served at 9 a. m., 3 p. m., and midnight. No hypoglycemic attacks were experienced while the above dietary regimen remained in effect.

A subtotal pancreatectomy was performed by one of us (R. K. G.); no tumor was found. Only by multiple section technique did the pathologist discover the tumor, which was lying in the tail of the pancreas. The postoperative course was complicated by a mild pneumonitis. The patient recovered well and has remained in good health to the present date.

CASE 2.—A 47-year-old white Russian housewife was hospitalized under the care of Drs. R. T. Woodyatt and L. K. Campbell because of progressively frequent frontal headaches and drowsiness followed by coma. The patient was well until 10 years prior to admission, when morning frontal headaches associated with profuse sweating and drowsiness developed. These symptoms always occurred in the early morning hours about once a week but could be prevented if the patient was awakened at 5 a. m. to drink a glass of orange juice. Four years prior to admission the patient was found comatose and in

6. Joslin, E. P., and others: Treatment of Diabetes Mellitus, ed. 8, Philadelphia, Lea & Febiger, 1946, p. 181.

7. (*a*) Brunschwig, A., and Allen, J. G.: Specific Injurious Action of Alloxan upon Pancreatic Islet Cells and Convoluted Tubules of Kidney, Cancer Research **4**: 45-54 (Jan.) 1944. (*b*) Mellinghoff, C. H.: Alloxan and Hyperinsulinism, Zentralbl. Chir. **77**: 66-72, 1952.

8. (*a*) Brown, H.: Hargreaves, H. P., and Tyler, F. H.: Islet-Cell Adenoma of Pancreas: Metabolic Studies on Patient Treated with Corticotropin and Cortisone, A. M. A. Arch. Int. Med. **89**: 951-960 (June) 1952. (*b*) McQuarrie, I., and others: Further Studies on Effects of ACTH on Spontaneous Hypoglycemosis, in Mote, J. R.: Proceedings of the Second Clinical ACTH Conference, New York, Blakiston Company, 1951, vol. 2, pp. 69-80. (*c*) Osnes, M., and Thorsen, R. K.: Islet Cell Tumors with Hyperinsulinism, Acta chir. scandinav. **105**: 227-242, 1953.

a cold sweat. After emergency hospitalization elsewhere, her symptoms were immediately relieved by intravenous dextrose administration. She was discharged and advised to take some form of nourishment frequently to prevent recurrent attacks. Because of several episodes of recurrent drowsiness terminating in coma when the patient missed her breakfast, she was admitted to the hospital for further investigation.

Physical examination showed an obese white woman lying comfortably in bed, rational and cooperative. Her weight was 198 lb. (90 kg.), pulse rate 70 beats per minute, temperature 97 F, respirations 20 per minute, and blood pressure 140/98 mm. Hg. The general physical and neurological examinations were within normal limits except for the presence of obesity and hypoactive patellar reflexes.

The blood cell count, urinalysis, and serologic studies showed normal results. The fasting blood sugar level was 30 mg. per 100 cc. on several occasions. Three basal metabolism tests gave rates of –7, –9, and –11%. The visual fields were normal. Two eight-hour glucose tolerance tests were as follows (hourly readings in mg. per 100 cc.): 80, 100, 120, 130, 110, 80, 60, and 60, and 130, 220, 230, 80, 80, 60, 50, and 50. Skull roentgenograms showed some erosion of the posterior clinoid process, which appeared to be pushed forward suggesting tumor.

Hospital Course.—The patient was given a 1,224 calory weight reduction diet (carbohydrate 150 gm., protein 83 gm., and fat 73 gm.) yielding 14 Cal./kg. served precisely at 6 a. m., 12 noon, and 6 p. m. Complementary feedings were served at 9 a. m., 3 p. m., 12 midnight, and 5 a. m. Several hypoglycemic attacks were observed in the morning when the patient failed to take her 5 a. m. feeding. All attacks were immediately relieved by administration of 50% dextrose solution intravenously. The patient received 3,000 r radiation therapy to the pituitary gland and was discharged and given the above diet.

No hypoglycemic attacks were experienced for 10 days after discharge. Shortly thereafter several episodes of hypoglycemia occurred that terminated in coma. She was hospitalized for the second time.

The results of the physical and laboratory examinations were essentially unchanged since her previous admission. A subtotal pancreatectomy was performed by Dr. V. C. David. All of the organ lying to the left of the superior mesenteric vessels was removed. Pathological examination showed no abnormalities of the islet cells. Ten days postoperatively the patient again became symptomatic with blood sugar levels less than 50 mg. per 100 cc. Rigid adherence to the diet schedule was necessary in order to prevent additional hypoglycemic attacks.

Alloxan Administration.—Drs. R. T. Woodyatt and L. K. Campbell cared for the patient during this time. The patient was maintained on a quantitative diet of 1,224 calories (carbohydrate 150 gm., protein 83 gm., fat 73 gm.) yielding 14 Cal./kg. served in three meals with in-between feedings providing nourishment every three hours. Three courses of alloxan therapy, each of three days' duration, were then administered. Alloxan (150 mg./kg.) in 0.9% sodium chloride solution was given intravenously at 3 ml. per minute each day during the first course. Alloxan (250 mg./kg.) in distilled water was administered intravenously daily during the second and third courses. A period of four to six weeks intervened between each course of alloxan therapy. Analysis and observations were made on the urine, and blood was obtained at six-hour intervals. The results are shown in the table. Following the third course of alloxan therapy, daily six hour quantitative urine and blood sugar determinations were carried out for two months. No significant variations of blood and urinary sugar level was observed from those recorded during the three courses of alloxan therapy. There was temporary evidence of liver damage after the third course; the Hanger test gave results of 3+, and the prothrombin time was 50%. The evidence of damage disappeared one month later. The nonprotein nitrogen level was not altered, and the urine remained free of albumin and cells. From clinical observations alloxan, in the doses administered, did not favorably affect the course of this patient's disease. In fact, several hypoglycemic reactions were noted during actual alloxan administration. These symptoms were immediately relieved by milk or orange juice given orally.

The following preparations were also administered without apparent benefit: (1) 2 cc. of growth hormone (anterior pituitary diabetogenic preparation) daily for 12 days; (2) adrenal cortex extract, 5 cc. every six hours for 24 days; (3) thyroid extract, 2 grains four times a day for 8 days; and (4) liver extract, 2 cc. per day for 22 days.

Results of Urinalysis and Laboratory Tests After Administration of Alloxan in Patient in Case 3

Date	Alloxan Given Intravenously, Gm.	Rate of Administration, Ml./Min.	24 Hr. Urine Volume, Ml.	Specific Gravity	Urine Sugar, Gm./24 Hr.	Acetone	Diacetic Acid	Average Blood Sugar Level, Mg./100 Cc.	Comment on Condition After Alloxan Course
						Course 1			
6/29/44	12	3	1,960	1.015	0.44	0	0	45	Asymptomatic; Hanger test negative; prothrombin time 100%.
6/30/44	12	3	2,080	1.018	0.48	0	0	45	
7/ 1/44	12	3	2,640	.....	0.41	0	0	22	
						Course 2			
11/17/44	20	3	3,000	1.007	0.61	0	0	70	Hypoglycemic reaction relieved by ingestion of milk; Hanger test negative; prothrombin time 100%.
11/18/44	20	3	5,500	1.010	1.07	0	0	70	
11/19/44	20	3	6,960	.....	0.77	0	0	60	
						Course 3			
1/24/45	20	3	3,900	1.015	0.78	0	0	50	Hypoglycemic symptoms during course relieved by ingestion of milk; Hanger test 3+; prothrombin time 50%; nonprotein nitrogen level 25.8 mg./100 cc.
1/25/45	20	3	4,380	1.010	0.44	0	0	100	
1/26/45	20	3	6,040	1.008	0.60	0	+1	70	

In a second operation performed by Dr. V. C. David, the remaining pancreas was excised except for a small portion in the region where the pancreatic duct enters the duodenum. An estimated 3 gm. of tissue was left. Pathological examination of the specimen again showed no tumor. The islet tissue appeared normal to slightly hypertrophic in spite of the previously administered large doses of alloxan. The patient received no benefit from this second operation, and hypoglycemic symptoms returned.

In a third operation done by one of us (R. K. G.), a total pancreatoduodenectomy was performed. No tumor was found at the operation. On multiple sectioning of the extirpated pancreatic remnant, the pathologist discovered an occult adenoma adjacent to the duodenum. Glycosuria appeared four hours after surgery. The patient died 30 hours postoperatively of pulmonary congestion.

CASE 3.—A 57-year-old white housewife complained of daily convulsions for three days prior to hospitalization on the service of Dr. L. Avery. She was well until eight years before hospitalization, at which time progressive nervousness and hyperirritability developed that were usually brought about by mental stress or overfatigue. Nervousness accompanied by rather profuse perspiration was most pronounced in the morning and would always be relieved in 30 to 40 minutes by the ingestion of food. During the three days prior to admission the patient was observed in a daily convulsion that terminated in coma.

Physical examination showed a well-developed, well-nourished white woman, rational and cooperative, lying quietly in bed. Her weight was 175 lb. (80 kg.), temperature 98.6, pulse rate

80 beats per minute, respiration 20, blood pressure 140/80 mm. Hg, and height 5 ft. 9 in. (175 cm.). The physical examinations showed normal results. The blood cell count and urinalysis, serologic, and spinal examinations gave normal results. The fasting blood sugar level (during convulsive attacks) was 18 mg. per 100 cc. A glucose tolerance test (hourly readings in mg. per 100 cc.) gave results of 30, 40, 40, 40, 30, and 30. The electroencephalogram showed distortion of alpha activity and abnormal, slow activity throughout. A big buildup was observed during overventilation. A roentgenogram of the skull was normal. A four hour corticotropin stimulation test showed a 50% eosinopenic response.

For the first 12 days in the hospital this patient was provided with a high protein, isocaloric fat, low carbohydrate, three meal diet with two complementary feedings at 10 a. m. and 3 p. m. During this period frequent hypoglycemic attacks were observed, all of which were immediately relieved by intravenous administration of 50% dextrose solution. The blood sugar levels during all attacks were below 50 mg. per 100 cc.

On the 13th hospital day, a low sodium general diet of three meals per day was offered and corticotropin and cortisone acetate therapy was begun. The clinical response to these hormones is illustrated in figure 4. The patient remained in good health, free from hypoglycemic symptoms so long as she received at least 25 mg. of corticotropin daily. Cortisone alone, 50 mg. per day for three days, failed to prevent convulsive

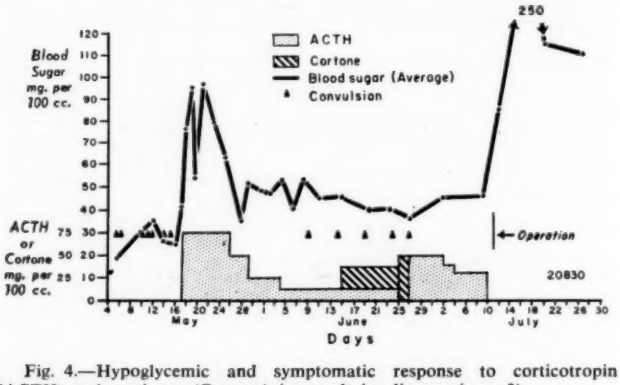

Fig. 4.—Hypoglycemic and symptomatic response to corticotropin (ACTH) and cortisone (Cortone) in occult insulinoma (case 3).

seizures. Cortisone, 25 mg., in combination with corticotropin, 10 mg., also proved ineffective in controlling the patient's symptoms.

A subtotal pancreatectomy was performed by Dr. R. K. Gilchrist. No tumor was seen at operation. An occult adenoma of islet cell origin, 12 mm. in diameter, lying in the tail of the surgical specimen was discovered by the pathologist. A rapid hyperglycemic rebound (250 mg. per 100 cc.) followed extirpation of the adenoma. This hyperglycemia persisted for nine days, gradually returning to normal. Seven years later this patient was in good health. The glucose tolerance curve was normal, and the fasting blood sugar level was 110 mg. per 100 cc.

COMMENT

Satisfactory dietary management was achieved in case 1 by providing an adequate caloric diet (27 Cal./kg.) served in three meals with complementary feedings providing nourishment every three hours. A reduction diet (less than 30 Cal./kg.) is often required. These patients are usually overweight because of excessive caloric intake caused by unsupervised frequent feedings empirically indulged in to prevent symptoms. The frequency of administration of an adequate caloric diet would appear to be more important in preventing symptoms than the quantitative character of the diet. The control of hypoglycemic symptoms in case 2 proved difficult in spite of a three hour feeding schedule, primarily because the patient was irresponsible and often missed her meals. Dietary management in case 3 was not effective because adequate feedings between meals were not provided.

Complementary intravenous alloxan therapy was instituted in case 2 because of the failure of the dietary therapy to control symptoms. Alloxan given intravenously, 100 to 250 mg./kg., did not appear to produce any beneficial effect. Indeed, during continuous administration several hypoglycemic reactions were observed that required the administration of sweetened orange juice to relieve symptoms. Relatively larger doses of alloxan (600 mg. to 1 gm./kg.) have been reported to produce transient favorable results in humans.[7a] This fact, together with our experience, would suggest that the human may be more resistant to this drug than dogs, and greater doses might be required to achieve favorable results. Considerable destruction of the beta cells has been observed by Böttger in a person who received alloxan (total dose 43.5 gm. or 637 mg./kg.) over a two month period.[9] Despite histological damage to the pancreatic beta cells, the frequency and severity of hypoglycemic attacks were not influenced by alloxan administration, and Böttger's patient died in a coma resulting from hyperinsulinism. Alloxan produces in dogs and rabbits injuries to the pancreatic islet cells and convoluted tubules of the kidney resulting in hypoglycemia and uremia. These toxic findings were not observed in the case of our patient who received alloxan therapy. Repeated nonprotein nitrogen studies showed no significant evidence of kidney damage. Necropsy examination of the thyroid, liver, heart, kidney, and pancreas disclosed no pathological changes attributable to alloxan toxicity.

Brunschwig [7a] has suggested that man's greater resistance to alloxan may be explained by the fact that in man alloxan is a component of the uric acid molecule, the end product of nucleoprotein metabolism, while in dogs and rabbits, further conversion of uric acid to allantoin takes place. Possibly in the latter metabolic system, alloxan is a factor that may produce a substance with selective affinity for pancreatic and renal epithelium.

Rachmiel Levine, in a personal communication, has suggested that the diabetogenic action of dehydroascorbic and dehydroisoacorbic acids alone or in combination with alloxan might offer more effective chemotherapeusis for spontaneous hyperinsulinism. Dehydroascorbic and dehydroisoacorbic acids are structurally and chemically similar to alloxan and probably produce diabetes in rats by interfering with the essential sulfhydryl enzymes of the beta cells.[10] The known synergistic action of ascorbic acid with alloxan may be the resultant dehydroascorbic acid production from the former. Permanent diabetes in rats may be produced by injection of either dehydroascorbic or dehydroisoacorbic acids.

Exogenous adrenocorticotropic hormone will produce hyperglycemia when given in sufficient doses. The administration of corticotropin, 25 mg. or more per day, proved beneficial by preventing hypoglycemic convulsions in case 3. Increasing the dose of corticotropin pro-

9. Böttger, H.; Römer, K., and Seitz, R.: Effect of Alloxan in a Patient with Tumor of Islands of Langerhans, Klin. Wchnschr. **30**: 507-510 (June 1) 1952.

10. Lazarow, A.; Patterson, J. W., and Levey, S.: Mechanism of Cysteine and Glutathione Protection Against Alloxan Diabetes, Science **108**: 308-309 (Sept. 17) 1948.

duced an increased blood sugar plateau. Ten mg. of corticotropin or 50 mg. of cortisone per day alone or in combination did not prevent hypoglycemic convulsions. The possible antagonistic action of these biological preparations when administered simultaneously may account for the failure in preventing hypoglycemic convulsions. It is possible that a larger dose of cortisone (more than 50 mg. per day) when administered parenterally might have had a beneficial effect.

Brown [8a] points out that a relatively greater dose of cortisone is required to control hypoglycemic symptoms in the same patient previously maintained asymptomatic on smaller doses of corticotropin. He observed that corticotropin, 15 mg. per day, when administered intravenously was sufficient to control symptoms in a patient with functioning islet cell adenoma. However, in the same patient 100 mg. of cortisone was required to prevent the appearance of symptoms. Brown further observed that 15 mg. of corticotropin intravenously given over 12 to 16 hours provided a greater hyperglycemic response than 120 mg. given intramuscularly.

The mechanism of action to increase blood sugar is not clear. It is well known that the temporary diabetes produced by corticotropin and cortisone is relatively insensitive to insulin. Kendall [11] has demonstrated the hyperglycemic effect of cortisone in depancreatized animals in instances in which insulin was no longer a factor. It would appear that the beneficial effect of these hormones may be derived from a peripheral insulin antagonism rather than from a central decrease in the insulin production of the pancreatic adenoma. It does not seem likely that the quantitative carbohydrate made available by the catabolic effect of corticotropin or cortisone on protein is responsible for the hyperglycemia. This amount is small and according to Conn [12] is not necessarily related in time or degree to protein destruction.

Successful long-term administration of corticotropin for spontaneous hypoglycemosis has been reported.[8b] Institution of corticotropin or cortisone long-term therapy for the management of organic hypoglycemia not remedied by surgery would appear to offer a means of favorable palliation. The undesirable complications of prolonged hormone therapy resulting in electrolyte, carbohydrate, and other metabolic disturbances should not seriously detract from the desirability of instituting long-term therapy in cases in which surgical treatment is inexpedient. The prime indication for the use of these biological preparations in control of spontaneous hypoglycemia would appear to reside in short-term preoperative therapy, particularly in patients whose symptoms cannot be adequately controlled by dietary means.

SUMMARY

Medical management of spontaneous hypoglycemia is important in the period before an operation is performed. In three cases of spontaneous hypoglycemia ultimately treated by surgery, preoperative and interim responses to dietary, alloxan, corticotropin (ACTH), and cortisone therapy showed some remission of symptoms.

A high protein, variable fat, and low carbohydrate diet served in three meals with complementary feedings providing nourishment every three hours is the most expedient management that may control hypoglycemic symptoms. The use of alloxan intravenously (150 to 250 mg./kg.) proved totally ineffective in controlling hypoglycemic convulsions. Corticotropin 25 to 75 mg., controlled hypoglycemic convulsions; cortisone, 50 mg., alone or in combination with corticotropin failed to prevent symptoms. Surgical excision of the islet cell adenoma remains the treatment of choice in spontaneous hypoglycemia of pancreatic origin.

1753 W. Congress St. (12) (Dr. dePeyster).

11. Kendall, E. C.: Hormones of Adrenal Cortex, Endocrinology **30**: 853-860 (June) 1942.

12. Conn, J. W.; Louis, L. H., and Wheeler, C. E.: Production of Temporary Diabetes Mellitus in Man with Pituitary Adrenocorticotropic Hormone: Relation to Uric Acid Metabolism, J. Lab. & Clin. Med. **33**: 651-661 (June) 1948.

NICKEL POISONING

II. STUDIES ON PATIENTS SUFFERING FROM ACUTE EXPOSURE TO VAPORS OF NICKEL CARBONYL

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Studies were recently reported by us [1] on the effects of acute and subacute exposure of experimental animals to the vapors of nickel carbonyl. In this paper are reported the results of clinical investigations on two groups of people exposed to this material: one group consisted of about 100 workmen exposed within a period of a few hours while engaged in the repair of a plant reactor contaminated with nickel carbonyl [2]; the other group consisted of five subjects exposed individually under varying working conditions and at different times and locations.

Nickel carbonyl was discovered by Mond, Langer, and Quincke [3] in 1890, and its extremely toxic nature was recognized shortly thereafter. In 1891 McKendrick and Snodgrass [4] concluded that a concentration of even less than 0.5% in air was dangerous. Later investigations have shown that this value is much too high and that the lethal concentration is about in the same range as that of hydrogen cyanide. The maximal allowable concentra-

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3. Mond, L.; Langer, C., and Quincke, F.: Action of Carbon Monoxide on Nickel, J. Chem. Soc. London **57**: 749-753, 1890.

4. McKendrick, J. G., and Snodgrass, W.: On Physiological Action of Carbon-Monoxide of Nickel, Brit. M. J. **1**: 1215-1217, 1891.

tion of nickel carbonyl was set at one part per million in air by the American Conference of Governmental and Industrial Hygienists in 1948.[5]

In our previous study on experimental animals [1] it was shown that $L.D._{50}$ values for 30 minutes' exposure for mice, rats, and cats are about 10, 35, and 270 parts per million by volume, respectively. Studies of the subacute toxicity in these animals indicated that the toxic effects were not cumulative and that tolerance could develop after exposure to sublethal concentrations. In addition, these studies indicated that the administration of dimercaprol (BAL) to rats exposed to nickel carbonyl increased their tolerance to this material by a factor of two.

SYMPTOMS AND PATHOLOGICAL CHANGES

The symptoms in humans suffering from acute exposure to nickel carbonyl have been described by Armit,[6] Amor,[7] Bayer,[8] Brandes,[9] Carmichael,[10] and others.[11] There is general agreement that the symptoms of acute poisoning are of two types, initial and delayed. Even with exposure sufficiently severe to cause death, the initial symptoms are usually mild and not specific, disappearing quickly on removal of the subject to uncontaminated air. Initial symptoms generally include frontal headache, dizziness, and sometimes nausea and vomiting. In the delayed reaction, tightness in the chest, cough, dyspnea, weakness, and gastrointestinal symptoms are frequently observed. According to Amor,[7] the delayed reactions are ushered in by the development of retrosternal pain. The respiratory rate appears to be a useful guide in predicting the severity of the exposure. In the severer cases, the respiratory rate is increased out of proportion to the pulse rate, so that a pulse-respiratory ratio of 3:1 or less during the initial stage suggests that the person may go into the delayed stage. A review of 354 cases by the Mond Nickel Company gives the following symptoms in the severe cases in their order of frequency: 56% of the patients complained of frontal headache, 42% giddiness, 33% tightness in chest, 28% nausea, 22% weakness of the limbs, 16% perspiring, 15% cough, 14% vomiting, 9% cold and clammy skin, and 9% shortness of breath.

There are relatively few descriptions in the literature of the pathological findings in cases of acute poisoning with nickel carbonyl. Amor,[7] Bayer,[8] and Brandes [9] have reported autopsy studies in cases of human exposure; Armit,[6] Barnes and Denz,[12] and Kincaid, Strong, and Sunderman [1] have studied the changes occurring in the organs of experimental animals exposed to lethal concentrations of the vapor.

The main pathological changes occur in the lungs, liver, and brain. The cause of death is regarded as being primarily due to loss of aerating tissue in the lungs. Throughout the lungs, areas of hemorrhage, atelectasis, and necrosis are frequently found. The pulmonary epithelium may become severely damaged. Bayer [8] reports that in his cases the alveoli were filled with a filamentous, coagulated material containing few erythrocytes and practically no leukocytes. Infiltration of connective tissue into the lungs is also reported by him.

Barnes and Denz [12] made a careful study of the tissues of rats and rabbits after the inhalation of nickel carbonyl in lethal or near-lethal concentrations. Their studies left little doubt that the primary cause of death was due to severe damage to pulmonary tissue. In their animals extensive pulmonary edema developed within a couple of hours after exposure. This was followed by capillary congestion, interstitial edema, and dilatation of the lymphatic vessels. After the fourth day, the pulmonary edema regressed and the alveoli became invaded with leukocytes, macrophages, and fibroblasts. It should be especially noted that Barnes and Denz [12] observed that the normal thin alveolar wall in the lungs of their animals was replaced by a remarkably thick, cellular structure of young connective tissue, which appeared to reach a maximum infiltration about three months after exposure and "then slowly resolved." They noted that rats examined a year or more after exposure did not show the presence of excessive fibrous tissue or other evidence of damage to the lung.

Kincaid, Strong, and Sunderman [1] report the deposition of brownish-black noniron staining pigment throughout the alveolar walls of the lungs in their experimental animals that died a few hours after exposure. Armit [6] indicated that probably the most outstanding pathological change observed in his exposed animals was degeneration of the endothelial cells of capillary vessels. Barnes and Denz suggest that the pulmonary damage may be caused by abnormal enzymatic activity in the capillary endothelium.

Except congestion, no unusual changes have been reported in the liver after human exposure; on the other hand, extensive degenerative changes with necrosis about the central veins are found histologically in liver sections from exposed animals. Kincaid and his associates [1] found brownish-black pigment deposited in the hepatic cells of rats. This pigment was similar to that also found in the lungs. Several cases have been reported in human beings in which extensive damage occurred to the brain. Dilated vessels and hemorrhages have been reported as well as the suffusion of the meninges with blood.[13] Armit [6] observed petechial hemorrhages in the adrenal glands of his exposed animals. These hemorrhages were found most frequently in the medullary portions of the glands.

Within recent years the high incidence of carcinoma of the respiratory passages among workers of long service in nickel refineries has come to be recognized.[14] Ac-

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12. Barnes, J. M., and Denz, F. A.: Effect of 2-3 Dimercapto-Propanol (BAL) on Experimental Nickel Carbonyl Poisoning, Brit. J. Indust. Med. **8**: 117-126, 1951.
13. Amor.[7] Brandes.[9]
14. (*a*) Hueper, W. C.: Occupational Tumors and Allied Diseases, Springfield, Ill., Charles C Thomas, Publisher, 1942, pp. 417-418. (*b*) Løken, A. C.: Lung Cancer in Nickel Workers, Tidsskr. norske lægefor. **70**: 376-378, 1950.

cording to Hueper,[14a] the apparent carcinogenic property of nickel carbonyl was first observed by Baader in 1924 and the first report that an excessive number of cases of carcinoma of the lungs and nasal passages developed among nickel workers was made by Grenfell in 1932.

An analysis of death certificates issued in South Wales between 1907 and 1934 indicated that 34% of the cases of cancer of the respiratory organs in South Wales occurred in nickel workers.[14a] Barnett [15] noted that, from 1923 to 1948 inclusive, 49 cases of cancer of the nose with 46 fatalities and 82 cases of cancer of the lungs with 72 fatalities were reported from a nickel works in England. The average number of years worked before the development of cancer was 23 for patients with nose cases and 25 for patients with lung cases.

CLINICAL OBSERVATIONS

Within recent months an opportunity was afforded to study a group of persons exposed to nickel carbonyl during the repair of a reactor in an oxo plant of one of the large oil refineries in Texas.[2] The reactor was surrounded by a stall that hindered the dispersal of fumes. Only persons who entered this stall became ill. The length of exposure within the stall varied from about 12 hours to a few minutes. A total of about 100 men were exposed, 31 required hospitalization, and 2 of these died.

In this accident, it appears clear that the patients were exposed essentially to the vapors of nickel carbonyl and not carbon monoxide. These cases, therefore, differ from many of those described in the early literature in which the toxic agent was presumably a mixture of nickel carbonyl and carbon monoxide. Evidence to support the diagnosis of nickel carbonyl poisoning without simultaneous carbon monoxide exposure are the following: 1. Air samples taken on three occasions during the period of exposure were all found to be free of carbon monoxide. 2. A careful study of the operating conditions that existed at the time of the accident showed that the carbon monoxide that did not form nickel carbonyl had been vented into a stack before the workmen entered the contaminated area. 3. Clinically, the men did not reveal any discoloration of the skin and mucous membranes suggestive of carbon monoxide poisonings.

Only a synopsis of the clinical observations will be given at this time.[16] The symptoms observed in the hospitalized men were characteristically of the initial and delayed types. The most prominent initial symptom after exposure was dizziness accompanied by a severe, throbbing headache. In more than one-half of the hospitalized cases, the men became nauseated after exposure and many of them vomited. Soon after exposure, most of the men experienced a sense of constriction in the chest with concomitant shortness of breath and dry, hacking, unproductive cough. In only one patient was a history of productive cough elicited.

In a number of the patients, the initial symptoms merged gradually into the more severe, delayed reactions; in others, the transition from one stage to another was more abrupt. Usually, the severe stage was begun by a paroxysm of coughing. The onset of the severe symptoms varied from 10 hours to 8 days after exposure.

A universal complaint of the critically ill men was that of extreme weakness and ready fatigue. Most of the men were too weak to turn over in bed. Some stated that they felt too exhausted to breathe. In a high percentage of cases, respirations could not be sustained without pressure oxygen therapy. Breathing was rapid, shallow, and panting in type. Respiratory rates above 60 per minute were observed in certain patients. Several of the critically ill patients had symptoms referable to the central nervous system. The two men who died had convulsions terminally; others became irrational.

None of the hospitalized men had any discoloration of the skin or mucous membranes initially, although most of them had cyanosis with the onset of the delayed symptoms. It might be mentioned that examination of the blood of several of the men spectrophotometrically five days after exposure revealed an absence of carboxyhemoglobin or any other abnormal pigments.

Diarrhea and abdominal distention occurred in several of the patients two or three days after exposure. This might suggest that nickel was being excreted by intestine in such cases, similar to the diarrhea that frequently follows metallic poisoning, such as arsenic. Drinker and others [17] observed that nickel ingested by human beings is largely excreted by intestine.

Fever was not a prominent symptom even in the critically ill patients. With few exceptions, the temperature of the sick men was not elevated above 101 F. Almost all of these had a moderate leukocytosis of 10,000 to 15,000 leukocytes per cubic millimeter. Hepatic and splenic tenderness was observed in several of the more critically ill patients, and several of them showed minimal jaundice. All of the hospitalized patients except the one who died four days after exposure received dimercaprol. The dimercaprol dosage was 2.5 mg. per kilogram of body weight every four hours for a total of six doses. Since the diagnosis of nickel carbonyl poisoning was not made until four days after exposure, none received dimercaprol earlier than the fifth day. It is our considered opinion that the administration of dimercaprol was beneficial in practically all cases and may have been lifesaving in several.

In practically all of the patients convalescence was protracted. Examination of a number of the hospitalized men (20 of the 31) two months after exposure revealed the presence of slight cyanosis in some of them, and many of them still had residual tenderness over the hepatic and splenic areas. Practically all of the men examined during convalescence complained of tiredness and unusual fatigue on exertion. They volunteered the opinion that they were unable to undertake their work with the same vigor as prior to the accident. Two months after exposure, most of the men had unusually high pulse rates. These persons included heavy boilermakers, whose normal pulse rates are frequently below 70 per minute. However, without exception, pulse rates of the 20 men examined were over 80 per minute, and, in 10 of them, the pulse rates were over 100.

Concentration of Nickel in Urine.—The normal concentration of nickel in urine is found to be 1.1 mcg.

15. Barnett, G. P.: Annual Report of the Chief Inspector of Factories for the Year 1948, London, Her Majesty's Stationery Office, 1949.

16. Drs. L. R. Byrd Jr. and A. B. Christie of Port Arthur, Texas, are preparing a detailed analysis of the clinical observations.

17. Drinker, K. R., and others: Hygenic Significance of Nickel, J. Industrial Hygiene 6: 307-356, 1924.

per 100 ml., standard deviation ± 0.85. Much higher values are observed after exposure to nickel carbonyl. Available information on nickel excretion in urine after accidental exposure is summarized in table 1. This table includes data for 17 subjects studied by us and 2 subjects studied by Bayer.[8] Patients in cases 1 to 4 inclusive were exposed at different times and locations; patients in cases 5 to 17 inclusive were part of the hospitalized group described in the previous section of this paper.

Data are given in table 1 for two patients (cases 1 and 2) who were subjected to slight exposure. In both cases specimens of urine collected during an eight hour period beginning shortly after exposure had nickel concentrations of over 10 mcg. per 100 ml. No symptoms, initial or delayed, were observed in either case. In case 2 it may be noted that the concentration of nickel in urine had dropped to the normal range three days after exposure. These results point to the probability that excess nickel in urine will indicate exposure to nickel carbonyl vapor at levels too low to cause discernible acute symptoms.

TABLE 1.—*Concentration of Nickel in Urine After Exposure to Nickel Carbonyl*

Case No.	Symptoms	Mcg. per 100 Ml. Time After Exposure (Days) 1	2	3	4	5	6	7	8	Reference
1	None	11	...	...	..	...	..	...	...	This work
2	None	18	...	2.2	..	...	..	...	...	This work
3	Mild (no lost time)	27	...	...	..	...	..	...	2.4	This work
4	Moderate (lost time)	35	9.0	...	..	...	..	6.1	1.8†	This work
5	Severe (required hospitalization)	..	...	...	..	2.3	..	...	...	This work
6	Severe (required hospitalization)	..	...	...	..	37.0	..	...	...	This work
7	Severe (required hospitalization)	..	...	...	..	4.8	..	...	...	This work
8	Severe (required hospitalization)	..	...	...	..	9.5	..	...	...	This work
9	Severe (required hospitalization)	..	...	...	..	2.3	..	...	...	This work
10	Severe (required hospitalization)	..	...	...	..	41.0	..	...	...	This work
11	Severe (required hospitalization)	..	...	...	..	30.0	..	...	...	This work
12	Severe (required hospitalization)	..	...	...	..	14.0	..	...	...	This work
13	Severe (required hospitalization)	..	...	...	..	31.0	..	...	...	This work
14	Severe (required hospitalization)	..	...	...	..	14.0	..	...	...	This work
15	Severe (required hospitalization)	..	...	...	..	14.0	..	...	...	This work
16	Very severe (required hospitalization)	..	...	...	..	1.0	..	...	...	This work
17	Fatal (13 days)	..	...	...	..	2.4	..	...	...	This work
18	Fatal (5 or 6 days)	..	...	...	..	52.0*	..	...	...	Bayer [8]
19	Fatal (4 days)	..	...	...	400*	...	..	...	...	Bayer [8]

* Postmortem specimen. † 13th day.

In case 3, the patient had only mild symptoms and lost no working time. In case 4, the patient had moderate symptoms and lost working time but did not require hospitalization. The concentration of nickel in the urine in both cases exceeded 25 mcg. per 100 ml. for specimens collected during the eight hours after exposure. In case 4 the value was still over 6 mcg. per 100 ml. of urine 7 days after exposure but dropped to within the normal range when the urine was examined 13 days after exposure.

Unfortunately no data on the excretion rate of nickel in urine in severe cases (5 to 17 inclusive) are available for the first four days after exposure since these cases were not diagnosed as nickel carbonyl poisoning until the fourth day. Nickel analyses in urine are not listed in table 1 for the period after the sixth day since the excretion of nickel was modified during this period by dimercaprol therapy (fig. 1).

In the severe cases (5 to 17 inclusive) that we studied, 12 out of 13 patients had values for nickel in urine above the normal range. The mean of these 12 cases is 17 mcg. per 100 ml. with a maximum of 41. None of our values are as high as those reported by Bayer [8] on samples obtained post mortem (cases 18 and 19).

From these studies it is concluded that the concentration of nickel in urine is high for at least 24 hours after exposure to nickel carbonyl, and that this concentration can probably be correlated with severity of exposure. Five days after severe exposure the concentration of nickel in urine is still usually very high, but exceptions may be found; indeed these exceptions occurred in two of our most critically ill patients, one of whom died.

Effect of Dimercaprol Therapy.—It was observed during this study that dimercaprol therapy increases the concentration of nickel in urine after nickel carbonyl exposure. Data are available for three categories classified according to the time elapsing between exposure and the beginning of therapy. In the first category (case 20, fig. 1) therapy was started less than 24 hours after exposure. In the second category (cases 5 to 17 inclusive of table 1) therapy was delayed five days, while in the third category (17 cases) the patients received dimercaprol therapy beginning more than five days after exposure.

The only patient (case 20) who received prompt therapy was a chemist exposed during the course of research work. Acute effects were observed on the evening after exposure, and dimercaprol therapy was started the following day. Urine collected during the first day of dimercaprol administration was found to have nickel at a concentration of 1,900 mcg. per 100 ml. The concentration then returned rapidly to normal, as shown in figure 1. For this case, the nickel in the urine is equivalent to 60 ppm of nickel carbonyl vapor in 200 liters of air. This amount of air would be inhaled in about 30 minutes. The patient lost working time but did not require hospitalization.

Data for the 13 patients of the second group (cases 5 to 17 inclusive), are also presented in figure 1. The data show that dimercaprol therapy increased the concentration of nickel in urine in 10 of the 13 cases. The largest increases were observed in the severest cases. Concentrations of over 10 mcg. of nickel per 100 ml. were found in the urine of 12 of the 13 patients.

In the third group, the concentration of nickel in urine before the administration of dimercaprol ranged from 5 to 0.4 mcg. per 100 ml. with an average of 2.2 In most cases, significant increases did not occur after dimercaprol administration. In two cases, however, sharp increases in the concentration of nickel in urine were noted after therapy. In one case the increase was from 1.6 mcg. per 100 ml. of urine to 51 after therapy. The corresponding figures for the other patient were 1.8 and 29 mcg. per 100 ml.

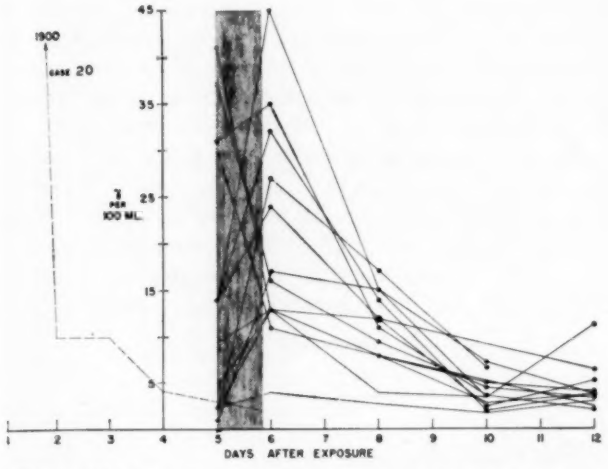

Fig. 1.—Nickel in the urine after dimercaprol therapy. Dimercaprol therapy was begun less than 24 hours after exposure in case 20; in the other cases, therapy was not begun until the fifth day because of delayed diagnosis. The shaded area represents the period during which dimercaprol was being administered.

Data available for three cases, (17 to 19 inclusive) are summarized in table 2. The high concentration of nickel in the lung and kidney tissues obtained in the two cases (18 and 19) reported by Bayer [8] can be compared to the low values for case 17 studied by us. These findings provide further evidence that dimercaprol aids in the elimination of nickel after nickel carbonyl exposure. No nickel was found in liver tissue in any of the three cases studied.

TABLE 2.—*Nickel Concentration in Tissues from Three Persons who Died After Nickel Carbonyl Exposure*

Case No.	Mcg. per 100 Gm. Wet Weight of Organ: Organs: Lung	Liver	Kidney	Reference
17	0.4	0	0.4	This work
18	...	0	55	Bayer [8]
19	22	0	106	Bayer [8]

Concentration of Nickel in Blood.—The concentration of nickel in oxalated blood was determined in cases 5 to 17 inclusive. Specimens collected on the fifth day after exposure, before dimercaprol therapy, were found to vary widely in nickel concentration. The values averaged 63 mcg. of nickel per 100 ml. of blood and ranged from 16 to 225. After dimercaprol therapy, the highest value was 33 mcg. per 100 ml.; the mean was 11. Individual values as well as the mean, decreased during therapy. The normal range of values for the concentration of nickel in blood is not well established, but a preliminary determination indicates that the mean value of 11 mcg. per 100 ml. is probably within the normal range.

Necropsy Findings in Case 17.—This patient, a muscular white man 29 years of age, a pipe fitter by occupation, died 13 days after exposure to nickel carbonyl. The details of the autopsy findings will not be given here.[16] The main pathological changes were found in the lungs, which contained many consolidated areas and only a small amount of aerating tissue. The pleura was thickened with subacute inflammation and edema. The lung tissue showed extensive deposition of fibrinoid material and infiltration of young fibrous tissue into the alveolar walls. This young tissue showed marked fibroblastic activity. In some areas the alveolar walls were only moderately thickened; however, in most places the pulmonary parenchyma was found to be practically consolidated with fibroblasts (fig. 2). In certain sections of the lungs large numbers of histiocytes were found in the alveolar spaces. These cells were laden with a granular brownish-black noniron staining pigment. The liver was essentially normal excepting for prominent Kupffer cells containing brownish-black noniron staining granules similar to those observed in the lungs. The adrenals appeared normal grossly and histologically. Except moderate perivascular edema, the brain sections appeared normal.

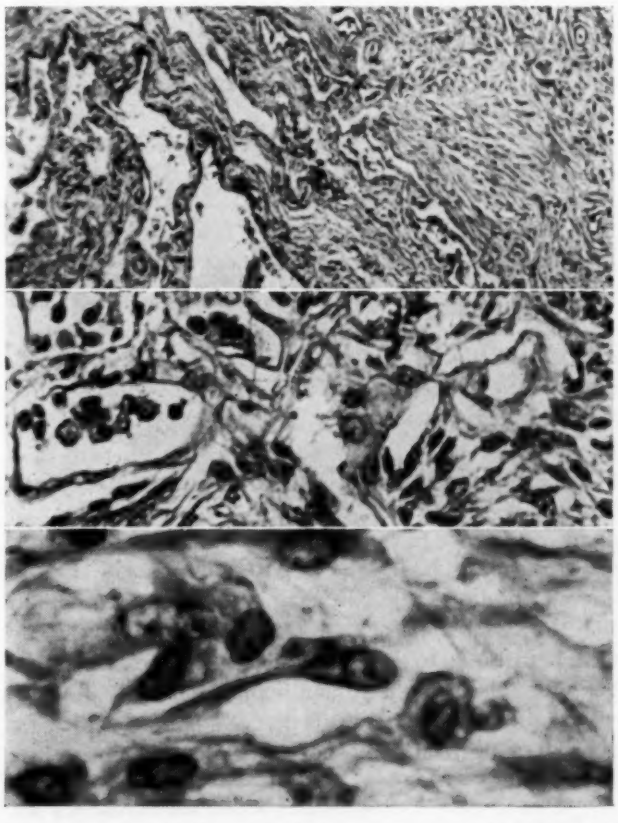

Fig. 2.—Low and high power fields of lung tissue showing marked fibrous tissue infiltration 13 days after exposure to nickel carbonyl. In large areas of the lungs the pulmonary parenchyma was practically consolidated by fibroblastic material.

COMMENT

The mechanism of the toxic action of nickel carbonyl has never been adequately explained. Amor [7] held the view that nickel carbonyl passed through the pulmonary epithelium unchanged. It is difficult, however, to recon-

cile Amor's view with the known physical and chemical properties of nickel carbonyl. Nickel carbonyl is reactive with a variety of nitrogen and phosphorous compounds as well as most oxidizing agents. These known properties suggest that it is probably reactive with biological materials.

A number of investigators have found no carboxyhemoglobin in blood samples obtained after exposure to nickel carbonyl. The fact that no carboxyhemoglobin has been found does not constitute evidence that nickel carbonyl does not decompose in the lungs to yield carbon monoxide. This may be illustrated by the following example: Nickel carbonyl in a concentration of 0.4 mg. per liter of air 30 minutes is lethal for mice and rats and, according to our studies, may be presumed to produce toxic symptoms in man. This exposure may be estimated to produce a concentration of carbon monoxide in blood of 0.6 vol. %. This estimate assumes normal values for the volume of air breathed in 30 minutes (200 liters) and for the total blood volume (8 liters). It also assumes the quantitative absorption and dissociation of the nickel carbonyl as well as the complete absorption of the released carbon monoxide. The estimated value of 0.6 vol. % is within the range of concentration observed in normal persons.

SUMMARY

Clinical observations are reported on 36 persons accidentally exposed to the vapors of nickel carbonyl. Two patients died and many of the others were critically ill. The concentrations of nickel in urine and blood were determined in samples obtained from exposed persons. Our studies indicate that the nickel concentrations in urine and blood are increased manyfold above normal after exposure. Increase in the concentration of nickel in urine may be correlated with the severity of exposure. Dimercaprol (BAL) was administered to 32 exposed persons, 31 of whom survived. Insofar as we are aware, this is the first report of the use of dimercaprol in the treatment of nickel carbonyl poisoning. The administration was attended by an increased excretion of nickel in urine and a marked decrease in the concentration of nickel in blood. It is our considered opinion that the administration of dimercaprol was beneficial in practically all cases and may have been lifesaving in several.

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BACITRACIN NEPHROPATHY

REPORT OF A CASE OF ACUTE RENAL FAILURE AND DEATH

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Bacitracin, a polypeptide produced by Bacillus subtilis, was discovered in 1945 by Johnson, Anker, and Meleney.[1] The early enthusiasm that followed the demonstration of its potent antibacterial action was soon dampened by reports of the nephrotoxic action of this and related polypeptide antibiotics [2] both in experimental animals and in man.[3]

In nearly every reported case, clinicians observed transient urinary abnormalities when bacitracin therapy was extended over a few days. The resulting proteinuria, cylindruria, azotemia, and occasional oliguria usually were self-limited, but at times necessitated termination of therapy. A review of the literature fails to reveal any fatality attributed to this antibiotic, so that the description of the renal lesion in a human being is lacking.

The following case report is that of a patient with acute bacterial endocarditis. Renal failure unrelated to her primary disease developed in this woman after the institution of bacitracin therapy.

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REPORT OF A CASE

A 57-year-old white housewife entered Mt. Sinai Hospital for the first time on May 27, 1953, complaining of intermittent fever and weakness that had begun early in February of the same year. Prior to the present illness, the patient had been entirely well. She denied any history or previous manifestations of heart disease. In January, 1953, she underwent extraction of six teeth over a two week period because of chronic pyorrhea. Three weeks later, the patient noted the onset of weakness, fever, and generalized malaise. Examination by her physician revealed anemia, and liver and iron therapy was given with no apparent response. The woman was hospitalized at another institution for two weeks in the beginning of March with the diagnosis of bronchopneumonia. She was treated with three daily intramuscular injections of penicillin. One week after discharge, her symptoms returned and were associated with a temperature to 105 F. On readmission to the hospital, a blood culture was found to be positive for a nonhemolytic Streptococcus. Penicillin was administered intramuscularly for only one week, and the patient was discharged again. At home, she was given oxytetracycline (Terramycin), 2 gm. per day, but the fever, weakness, and malaise persisted. In April, a heart murmur was noted for the first time, and the patient complained of exertional dyspnea. One week prior to admission to Mt. Sinai Hospital, mild congestive failure developed, and on the day of hospitalization symptoms of a thrombophlebitis of the left leg became apparent.

Physical examination revealed a pale, chronically ill woman with a temperature of 101 F, regular sinus tachycardia of 102 per minute, respirations of 24 per minute, and blood pressure of 140/0 mm. Hg in both arms. Petechiae were seen over the

chest. The neck veins were flat, and the lungs were clear to percussion and auscultation. The heart was enlarged, with the point of maximum impulse in the anterior axillary line in the fifth intercostal space. A short, harsh systolic murmur and a longer, low-pitched diastolic murmur were heard at the apex. At the base, a loud, blowing diastolic murmur replaced the second sound and could be heard throughout diastole. A firm, smooth, nontender liver edge was palpable 2 cm. below the right costal margin. There was clubbing of the fingers, a trace of pretibial edema, and signs of acute thrombophlebitis in the left calf.

Fig. 1.—Close-up view of aortic valve showing darker areas representing hemorrhagic tips of calcified vegetations that replaced and distorted the valve cusps.

The laboratory findings on admission included a completely normal urinalysis; hemoglobin level of 12.5 gm. per 100 ml., and leukocyte count of 18,000 per cubic millimeter with 80% polymorphonuclear leukocytes. The sedimentation rate was 52 mm. per hour. The blood urea nitrogen was 12 mg. per 100 ml., and other blood chemistry findings were normal. A chest film revealed enlargement of the heart in its transverse diameter, but initial and subsequent electrocardiograms demonstrated no significant myocardial impairment.

Despite repeatedly negative blood cultures, it was felt that the clinical evidence of active bacterial endocarditis made the institution of vigorous antibiotic therapy mandatory. Treatment was begun with 4,800,000 units of penicillin and 1 gm. each of streptomycin and dihydrostreptomycin daily. In addition, bishydroxycoumarin was given for phlebitis, which subsided during the first three weeks. After that, bishydroxycoumarin was not given. High blood antibiotic levels were maintained for 30 days, during which time the patient also received probenecid (Benemid), 1 to 2 gm. daily, to aid in achieving an adequate serum penicillin level. All blood cultures remained sterile. The patient remained weak and febrile, and anemia, leukocytosis, and elevated sedimentation rate persisted. Congestive failure was mild throughout the course and was treated primarily by a low salt diet. The lack of response to vigorous antibiotic therapy was difficult to understand. There were no additional clinical features or laboratory evidence to suggest active rheumatic carditis as the cause of the persistent symptoms and signs. It was thought possible that the fever was induced by the drugs being given, so all medications were discontinued. The fever continued unabated.

At this point it was decided that bacitracin, 50,000 units per day given parenterally in five divided doses, should be added to the regimen.[4] The patient became afebrile within three days and remained so until the administration of bacitracin was terminated. Prior to this therapy, the patient's urinary output had been ample, her blood urea nitrogen had been normal, and repeated urinalyses had revealed only an occasional trace of albumen. On the third day after therapy with bacitracin was begun, proteinuria, oliguria, and azotemia developed. Simultaneous with the fall of the urinary output to 100 cc. per day, the blood urea nitrogen rose to 44 mg. per 100 ml. Because of the severe impairment amounting to almost complete renal shutdown, bacitracin therapy was discontinued after six days of treatment. The patient remained oliguric, voiding less than 300 cc. per day, and the blood urea nitrogen level continued to rise, reaching 76 mg. per 100 ml. two days after cessation of bacitracin therapy. As a supportive measure, three small transfusions of packed red blood cells were administered without incident. The patient failed to respond and became lethargic. A pericardial friction rub developed, and the woman died 10 days after the institution of bacitracin therapy.

The significant findings of the postmortem examination were in the heart, lungs, spleen, and kidneys. The pericardial cavity was obliterated by a fresh, shaggy, fibrinous exudate. The heart was enlarged, weighing 440 gm.; left ventricular hypertrophy accounted for most of the increase in weight. The aortic valve was largely replaced by fungating, calcified vegetations (fig. 1) that revealed softened, hemorrhagic areas. The left ventricular endocardium was thickened and opaque, with regurgitation "pockets" below the noncoronary aortic cusp, which was completely torn in half. The remainder of the heart, including the mitral valve, was unremarkable. There was no gross evidence of previous rheumatic disease. Postmortem cultures of blood and vegetations from the heart were sterile, and bacterial stains were negative. Microscopically, the vegetations appeared to be healing, as evidenced by fibrosis, calcification, and a cellular infiltrate consisting primarily of lymphocytes and plasma cells.

Fig. 2.—Photomicrograph showing the kidney in the case reported. Although glomerular structure is normal, necrosis, desquamation, and calcification of tubular epithelium is striking. Much of the intraluminal cast material reveals calcium deposition. Moderate interstitial edema and cellular infiltration caused separation of the tubular structures.

The myocardium revealed focal abacterial collections of polymorphonuclear leukocytes (Bracht-Wechter lesions), but no signs of previous rheumatic involvement.

There was scattered focal hemorrhagic bronchopneumonia, associated with minimal pulmonary edema, in both lower lobes of the lungs. There were multiple organizing infarcts in the

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spleen. Each kidney weighed 200 gm. Both capsules were stripped with ease and revealed pale, generally smooth surfaces. The consistency of the organs was softer than usual. On section, the cortex was pale but of normal thickness, and the medulla was dark brown. The corticomedullary junction was indistinct because of numerous fine grey streaks extending from the outer medulla into the inner cortex. Similar striations coursed through the columns of Bertini. The renal vessels and pelves were unremarkable. Aside from mild engorgement, the glomeruli in the

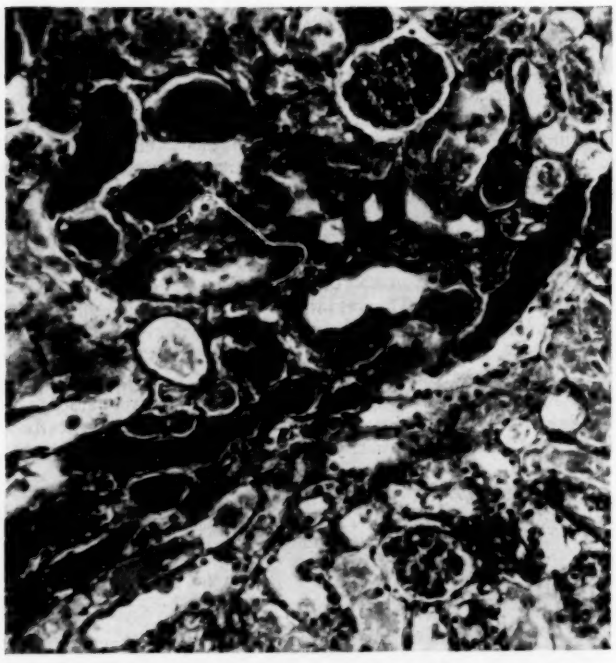

Fig. 3.—Photomicrograph showing a mild lesion of the kidneys of mice that received one intraperitoneal injection of 10,000 units of bacitracin per kilogram of body weight. Although casts occlude many of the proximal tubules, the lesion is less widespread and evidence of regeneration is present.

kidneys were normal, with the usual cellularity and clear Bowman's capsules. No Löhlein lesions were seen. There was mild arteriosclerosis and arteriolosclerosis, and the medium-sized vessels of the medulla were engorged. The tubules were strikingly abnormal. The lesions were most marked in the inner layer of the cortex and affected primarily the proximal convoluted tubules. The early lesion consisted of swelling and eosinophilia of the tubular epithelium. Some of these cells contained intracytoplasmic hyaline droplets. In the more advanced stages, the tubular epithelium had undergone necrosis and desquamation with cast formation. These casts were composed of nuclear and cytoplasmic debris and an eosinophilic homogeneous substance. This material did not stain uniformly with chromatrope aniline blue (Laroque). The von Kossa stain confirmed the presence of calcium mainly in the cast material, but also in the epithelial cells. There were many tubules with a low cuboidal epithelium and numerous mitoses as evidence of early regeneration. It was difficult to demonstrate a normal proximal tubule. The loops of Henle and the distal and collecting tubules contained occasional casts, but their epithelium was normal (fig. 2).

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COMMENT

Clinically the nephrotoxic effects of bacitracin have been described and studied. In treating 148 syphilitic patients with bacitracin given parenterally, Miller consistently noted proteinuria and cylindruria during therapy. Miller, McDonald, and Shock confirmed these findings in 12 normal men and also demonstrated impaired tubular function by renal clearance methods.[5] In the case reported here, the rapid onset of proteinuria without hematuria and the evidence of decreased renal function were not unexpected; however, the continuation of this process to severe oliguria with progressive uremia and death was unusual.

Renal lesions like those in our case have been seen in the experimental animal after the administration of polypeptides and single amino acids. Wachstein studied the kidneys of young rats after the administration of *dl*-serine and was able to show localization of the resulting lesion in the distal third of the proximal convoluted tubule.[6] Artom, Fishman, and Morehead demonstrated that the *d*-isomer of serine was the causative agent.[7] Similar lesions were seen by Scudi, Coret, and Antopol in their study of the toxicity of bacitracin in the experimental animal.[8]

To reproduce their findings, we set up the following experiments. Eighteen 42 gm. white mice were given bacitracin in varying dosages in a single intraperitoneal injection. Three similar mice served as controls. The dosage and time at which the animal died or was killed are noted in the table, and the renal lesions found are also graded 0 to 4 + in terms of the microscopic severity. All mice receiving 100,000 units per kilogram of body weight died within 20 minutes with renal abnormalities of a nonspecific shock lesion. Excluding this and the control group, the kidneys of the remaining mice all showed similar lesions varying only in severity.

Data on Experimental Mice Given Bacitracin

Mouse No.	Dose, Units/Kg.	Time of Death, Hr. After Injection	Severity of Lesion
1-3	0	48	0
4-9	100,000	Within 20 min.	Nonspecific shock-like
10-12	30,000	24	4+
13-15	30,000	36	4+
16, 17	10,000	24	2+
18, 19	10,000	48	2+
20, 21	10,000	120	1+

Grossly the kidneys were pale, markedly swollen, and boggy. Section revealed a pale, thick cortex and a dark red-brown, engorged medulla. With a hand lens, grey streaking, as seen in the kidneys of our patient, was readily evident in the same locations.

Microscopically (fig. 3) there was widespread tubular necrosis in the cortical and subcortical layers. In mice 16 and 17, in which the earliest lesions were best seen, eosinophilia and hyaline droplet formation were conspicuous. Other tubules showed necrosis and desquamation of the epithelial linings. Many of the distal tubules, loops of Henle, and collecting tubules were dilated by casts in the lumens, but revealed no intrinsic epithelial lesion. All glomeruli appeared normal except for occasional evidence of protein coagulum in Bowman's cap-

sule. Regenerating epithelium and mitoses were seen as early as 36 hours (group 4), and calcification of both cast material and tubular epithelium was noted as fine stippling after 48 hours, reaching a maximum in those mice killed after five days. These lesions are almost identical with those in our patient.

We ascribed the patient's renal failure to bacitracin and/or to the *d*-amino acids [9] it contains for the following reasons: 1. Renal impairment occurred immediately on the addition of bacitracin to the therapeutic regimen. Urinary output and constituents as well as pertinent blood chemistry findings had been normal prior to the use of this drug. 2. The only other source of therapy that could be implicated are blood transfusions and probenecid. These are unlikely causes of the renal impairment for several reasons. There was neither clinical nor pathological evidence that any transfusion incompatibility had taken place. Probenecid has been extensively appraised clinically and experimentally. Both acute and chronic toxicity experiments in animals and man failed to reveal any functional aberration or histological lesion caused by its use.[10] 3. The development of heavy proteinuria without hematuria one to two days after beginning bacitracin therapy is characteristic of the drug's nephrotoxic action as seen clinically and demonstrated experimentally. The unusual features here were the progressive uremia and oliguria that continued even after cessation of therapy. 4. Pathologically the lesions in the case reported were similar to those caused by bacitracin in the experimental animals.

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USE OF BALLISTOCARDIOGRAPHY IN EVALUATION OF PAROXYSMAL RAPID HEART ACTION

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The occurrence of an attack of paroxysmal rapid heart action nearly always arouses great concern in the patient and suggests to him the presence of serious heart disease. This condition invariably calls for an evaluation of the cardiovascular status of the patient. It is generally agreed that paroxysmal rapid heart action is fundamentally a functional disturbance, but one occurring in hearts that are structurally either normal or abnormal. Because of our routine use of ballistocardiography in the study of cardiovascular problems, it occurred to us that this method might be helpful in the evaluation and prognosis of cases of paroxysmal arrhythmia.

This communication is the report of a group of representative cases from our experience in hospital and office practice. All ballistocardiograms were taken with the Dock 2-coil electromagnetic pickup, using a 24-microfarad condenser. They were recorded by a Sanborn Viso-Cardiette.

CASE 1.—A 55-year-old man had a history of repeated attacks of paroxysmal auricular tachycardia. He was referred to the hospital for cardiovascular study by his family physician, who suspected organic heart disease. The first episode occurred about 10 years before admission. Before then the history was noncontributory. The physical examination showed no abnormalities. The roentgenogram of the heart showed normal outlines. An electrocardiogram made during periods of normal sinus rhythm showed only left axis deviation. The ballistocardiogram (see figure, *A*) showed normal results. The patient and his family physician were advised that there was no evidence of organic heart disease. Four months after the patient's initial admission, he died of encephalomalacia caused by cerebral thrombosis. At autopsy, the heart was grossly normal. A few of the microscopic sections of heart muscle showed slight fibrotic changes, while most of the sections were normal.

It is known that paroxysmal auricular tachycardia may be the first sign of coronary artery disease.[1] If attacks of paroxysmal auricular tachycardia develop in a man past 40, one must suspect coronary disease as the cause. In this particular patient the normal ballistocardiogram suggested that such a condition did not exist. An autopsy confirmed that impression.

CASE 2.—A 45-year-old white man was first seen in July, 1950. The history indicated that the first attack of paroxysmal rapid heart action had occurred one year previously. Two days before the examination he had another attack. There was a history of recent onset of diabetes. Examination showed moderate obesity, glycosuria, and a blood pressure of 150/90 mm. Hg. There was no cardiomegaly on physical examination or roentgenographic study, and auscultation of the heart showed no abnormalities. A 12-lead electrocardiogram taken while the patient was asymptomatic showed only left axis deviation. The ballistocardiogram was grossly abnormal, Brown grade 3 (See figure, *B*). The patient has had repeated follow-up examinations. To date no signs or symptoms of heart disease have developed. Attacks of paroxysmal tachycardia still recur several times a year. The electrocardiogram has remained normal, while several ballistocardiograms have shown persistent abnormalities.

While there is no proof that this patient has heart disease, the repeated finding of a markedly abnormal ballistic tracing strongly suggests that the function of the heart is impaired at all times. It is reasonable to suspect that heart disease does exist in this patient, and its clinical appearance would not be unexpected.

CASE 3.—A 61-year-old white man was hospitalized with an acute toxic psychosis secondary to morphine medication. Physical examination showed rapid, regular heart action. The electrocardiogram showed auricular flutter at a rate of 350 with 2:1 auriculoventricular block. Digitalization caused reversion to normal rhythm. The electrocardiogram was then repeated, and it showed changes compatible with a mild digitalis effect. The

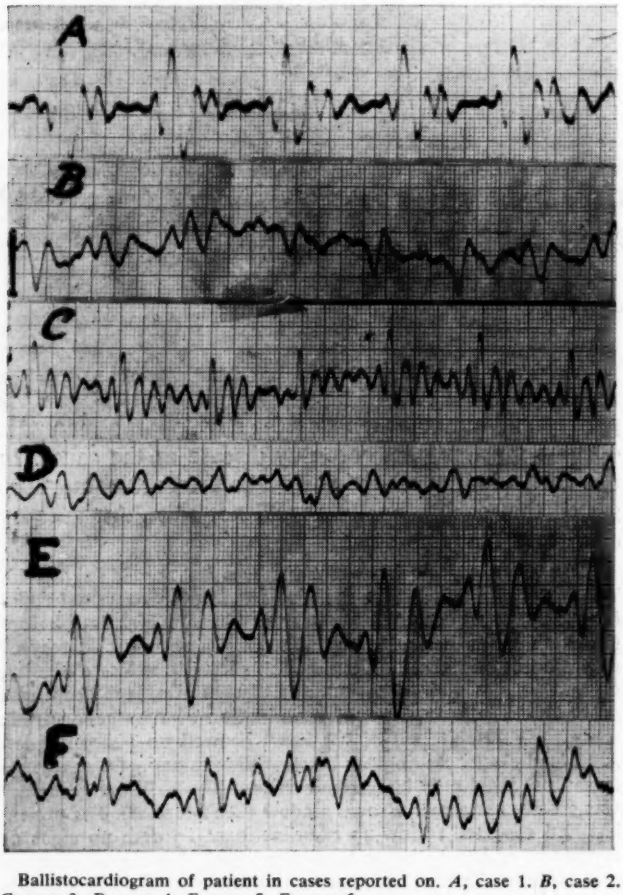
From the Veterans Administration Hospital.

1. Prinzmetal, M., and others: The Auricular Arrhythmias, Springfield, Ill., Charles C Thomas, Publisher, 1952, p. 46.

ballistocardiogram (see figure, *C*) two days after reversion to sinus rhythm showed normal results. The patient had nothing in the history or physical examination to suggest heart disease.

Generally speaking, auricular flutter is most often considered to be associated with structural heart disease. In this case it is safe to assume that the rhythm disturbance was secondary to the patient's toxic state and was not an expression of organic heart disease.

CASE 4.—A 52-year-old white man was given a preemployment examination on Jan. 15, 1952. The electrocardiogram showed auricular flutter at a rate of 300 with 2:1 auriculoventricular block. When the patient returned for a ballistocardiographic examination three days later, a normal sinus rhythm and a grossly abnormal ballistocardiogram were seen (see figure, *D*). He was not employed. Nine months later he was admitted to the



Ballistocardiogram of patient in cases reported on. *A*, case 1. *B*, case 2. *C*, case 3. *D*, case 4. *E*, case 5. *F*, case 6.

hospital with severe dyspnea, chest pain, weakness, and loss of weight. On physical examination he was found to be markedly dyspneic and cyanotic. The lungs were emphysematous. The heart was enlarged at roentgenographic examination. No murmurs were heard. The heart beat was rapid and regular at a rate of 150 beats per minute. Blood pressure was 140/80 mm. Hg. The liver was enlarged and tender. There was no peripheral edema. Dehydrocholic acid (Decholin) circulation time was 34 seconds. Vital capacity was 1.5 liters. An electrocardiogram showed auricular flutter at a rate of 300 with 2:1 auriculoventricular block. Cardiac failure increased, auricular flutter persisted, and the patient died on Dec. 29, 1952, in marked congestive heart failure. Permission for autopsy was denied.

2. Starr, I.: On Later Development of Heart Disease in Apparently Healthy Persons with Abnormal Ballistocardiograms: 8- to 10-Year Afterhistories of 90 Persons over 40 Years of Age, Am. J. M. Sc. **214**: 233, 1947.

This patient, who felt well enough to apply for employment, had paroxysmal auricular flutter with a grossly abnormal ballistocardiogram during a period of sinus rhythm. Shortly thereafter permanent auricular flutter with congestive heart failure developed, which terminated fatally. The grossly abnormal ballistocardiogram when the patient was first seen proved valuable in the proper evaluation of the case. This was confirmed by the subsequent clinical course.

CASE 5.—This 20-year-old white man had noticed sudden attacks of irregular heart action for several months. When seen on April 6, 1953, he was having paroxsymal auricular fibrillation at a rate of 170 per minute confirmed by electrocardiogram. Physical examination showed no abnormalities except for the arrhythmia. There was no roentgenographic evidence of cardiomegaly. Reversion to normal rhythm occurred while the patient was under observation four hours later. Reexamination on several occasions failed to show any evidence of heart disease. The ballistocardiogram (see figure, *E*) was entirely normal.

The patient continues to have occasional attacks of auricular fibrillation. The ballistocardiogram was a welcome confirmation of the clinical impression that no organic heart disease was present. There is a definite possibility that this patient's attacks are related to an allergy.

CASE 6.—A 51-year-old white female patient was first seen in 1950 complaining of irregular palpitation. Examination showed frequent premature auricular systoles. There was no hypertension or cardiomegaly and no evidence of valvular heart disease. The electrocardiogram showed normal results except for the premature beats. The patient was treated with phenobarbital and quinidine, and her condition improved. On May 26, 1950, she was seen at home because of sudden onset of severe cardiac irregularity and palpitation. She was hospitalized. The electrocardiogram showed auricular fibrillation. Reversion to normal rhythm occurred with quinidine therapy. Repeated ballistocardiograms have been grossly abnormal (see figure, *F*). Premature beats still occur intermittently, but paroxysmal auricular fibrillation has not recurred. To date other manifestations of heart disease have not developed.

The repeated demonstration of a grossly abnormal ballistocardiogram strongly suggests that organic heart disease is responsible for the auricular arrhythmia. It is likely that other manifestations of heart disease will develop in the future.

As stated previously, paroxysmal rapid heart action occurs in hearts that are structurally normal or abnormal. For a number of years cardiologists have used an orthodox set of criteria to determine whether structural heart disease is present or absent. If the history and physical examination are noncontributory, the electrocardiogram is normal, and the heart does not appear enlarged by careful x-ray study, it has been assumed that organic heart disease is absent. The use of ballistocardiography in clinical cardiology has brought about a change in this concept. The findings of Starr,[2] which were confirmed by others, taught us that heart disease may be suspected even before the above-named orthodox criteria appear whenever the ballistocardiogram is abnormal. Ballistocardiography has already proved valuable in the study of a number of cardiovascular conditions.[3] The cases described above represent examples of different types of paroxysmal auricular arrhythmias studied with the aid of ballistocardiography. Our experience suggests that ballistocardiography will prove a valuable adjunct to existing methods for the evaluation of patients who suffer from attacks of paroxysmal heart action. We are fully aware of the fact that we do not have autopsy reports to prove our belief that all patients with grossly abnormal ballistocardi-

ograms as the only clinical manifestation have organic heart disease. Our belief is strengthened by Starr's follow-up studies on apparently healthy persons with abnormal ballistocardiograms,[2] as well as by Dock's statement [4] that in his experience grossly abnormal ballistocardiograms (Brown, grade 3 or 4) are only found in cases of heart disease.

We intend to follow up our patients with auricular arrhythmias in an attempt to validate or disprove our present impression. The purpose of this report is to call attention to a new application of ballistocardiography and to encourage investigation of this problem on a larger scale.

3. Nickerson, J. L., and others: Diagnosis of Coarctation of Aorta with Aid of Low Frequency, Critically Damped Ballistocardiograph, Circulation **1**: 1032, 1950. Mandelbaum, H., and Mandelbaum, R. A.: Studies Utilizing Portable Electromagnetic Ballistocardiograph: III. Ballistocardiogram in Bundle Branch Block, ibid. **6**: 578, 1952. Mandelbaum, H., and Mandelbaum, R. A.: Studies Utilizing Portable Electromagnetic Ballistocardiograph: II. Ballistocardiogram as Means of Determining Nicotine Sensitivity, ibid. **5**: 885, 1952. Levin, S. L., and Selinger, A. G.: Value of Ballistocardiography in Neuropsychiatric Hospital: New Application of Method, J. Nerv. & Ment. Dis. **117**: 399, 1953. Starr, I., and Jonas, L.: Supernormal Circulation in Resting Subjects (Hyperkinemia), with Study of Relation of Kinemic Abnormalities to Basal Metabolic Rate, Arch. Int. Med. **71**: 1 (Jan.) 1943. Mandelbaum, H., and Mandelbaum, R. A.: Studies Utilizing Portable Electromagnetic Ballistocardiograph: IV. Clinical Significance of Serial Ballistocardiograms Following Acute Myocardial Infarction, Circulation **7**: 910, 1953. Scarborough, W. R., and others: Review of Ballistocardiography, Am. Heart J. **44**: 910, 1952. Dock, W.; Mandelbaum, H., and Mandelbaum, R. A.: Ballistocardiography in Medical Practice, J. A. M. A. **146**: 1284 (Aug. 4) 1951. Mandelbaum, H., and Mandelbaum, R. A.: Studies Utilizing the Portable Electromagnetic Ballistocardiograph: I. Abnormal HIKJ Patterns in Hypertensive and Coronary Artery Disease, Circulation **3**: 663, 1951. Mandelbaum, H., and Mandelbaum, R. A.: Clinical Findings with the Dock Ballistocardiograph, New York J. Med. **51**: 1834, 1951. Pordy, L., and others: Clinical Evaluation of the Ballistocardiogram: I. Normal Subjects, Am. Heart J. **42**: 321, 1951. Taymor, R. C., and others: The Ballistocardiogram in Coronary Artery Disease, J. A. M. A. **148**: 419 (Feb. 9) 1952. Gubner, R.: The Diagnosis of Arteriosclerosis, Including Observations on Lipid Metabolism and the Ballistocardiogram, Tr. A. Life Insur. M. Dir. America **34**: 20, 1950.

4. Dock, W.; Mandelbaum, H., and Mandelbaum, R. A.: Ballistocardiography: Application of Direct Ballistocardiograph to Clinical Medicine, St. Louis, C. V. Mosby Company, 1953, p. 163.

DE URINA

Homer W. Smith, Sc.D., New York

In her volume of short stories, entitled "Seven Gothic Tales," the Danish writer Isak Dinesen puts into the mouth of an Arab, sailing along the coast of Africa by starlight, the speculation: "What is man, when you come to think upon him, but a minutely set, ingenious machine for turning, with infinite artfulness, the red wine of Shiraz into urine?" When you come to think on him, man is many things, depending on your point of view. One may add that man is also an ingenious machine for unravelling the infinite artfulness of himself, and it will come as no surprise when I assert that the study of urine has contributed as much to this self-analysis as has the study of any other single feature of his body.

It was probably not until he abandoned the forest for the cave that man began to urinate into a pot and hence had the opportunity to discover that wine and water do, in fact, come to much the same end but to suspect that this mysterious liquid might have practical values beyond either wine or water. Only those persons on whom the Cromwellian period imposed the strictures of Puritanism have hidden the urinal under the bed; throughout most of history and for most living peoples urine has been and remains a respectable and sometimes valuable commodity.

EARLY USES OF URINE

In keeping with his primitive philosophy, man's earliest efforts to utilize what would otherwise go to waste was of course in witchcraft and magic, but with these applications we are not concerned. Of more interest to us is the use of urine in primitive medicine, for there is scarcely a disease that has not been treated with it, either by external application or internal administration. The therapeutic use of urine is attested in the Egyptian medical papyri, and many such applications are recounted by the Roman writer Pliny. These practices were not mere repetitions of morbid appetite but usually the logical application of the prescientific suppositions of the age. No less a man than Robert Boyle, the great 17th century pioneer in chemistry, is quoted as saying that the virtues of human urine, as a medicine, would require for their enumeration an entire volume. Sophistication does not always diminish faith; in France the wealthy ladies of Boyle's day took urine baths to beautify the skin, while the belief persists in rural communities today that urine will soften the hands and cure a variety of skin diseases.

Of still more interest than these unproved medicinal virtues is the use of urine in diagnosis and prognosis. Fragmentary records show that the Sumerian and Babylonian physicians gave attention to its color, consistency and frothiness, the presence of clouds and sediments, and casts and blood. Possibly as old as the Mesopotamian records are those of Hindu medicine, preserved in the writings of Charaka and Susruta, in which morbid conditions involving the urine are systematically divided into 20 varieties. The Hindus recognized prostatic hypertrophy and its sequel of urinary suppression, and they identified the disease diabetes mellitus by the name "honey urine." It had been observed that trains of black ants were attracted to the sweet urine, and thus these insects came to be recognized as a means of diagnosis—unquestionably one of the oldest reliable diagnostic tests.

The Egyptians mentioned urine as typical of a particular type of unpleasant odor and referred to certain diseases of the urinary bladder. They also noted involuntary emission in relation to spinal injuries, though none of the papyri mentions the examination of urine as an aid to diagnosis. In the Hippocratic texts, however, the characteristics of urine in disease are mentioned 182 times, and, as is typical of these texts, these characteristics are used both for diagnosis and prognosis. Galen praised Hippocratic medicine for its acute observations on urine but added nothing new to the notions of the Greeks.

With Paulus Aegineta of the seventh century, the examination of urine became more systematic and de-

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tailed, and in that century Theophilus mentioned the application of heat as a diagnostic test, referring to the cloudiness caused by heating albuminous urine. Avicenna in the 11th century pointed out the difference between urine passed in the morning and that passed at night, and remarked the influence of age, food, and drugs on its color, while early in the 12th century Alsaharavius cautioned the physician not to allow himself to be imposed on by the color of the urine, which may be affected by the patient's having taken saffron, cassia, or other drugs: "Such tricks," he says, "are often practiced upon water doctors." The expression "water doctors" implies that by this date the visual examination of the urine was becoming the specialty that, as uroscopy, was soon to spread over the whole of Europe.

Arising possibly in Persia, uroscopy was the art (if we may call it such) of making a diagnosis and prescribing therapy solely on the evidences afforded by the visual examination of the urine, for which purpose the fluid was studied carefully in a specially shaped flask and by an almost ritualistic procedure. Toward the close of the 12th century the Salernan physician, Gillis de Corbeil, wrote a long poem on uroscopy, entitled "Liber de Urinis" which served to popularize the practice, and for several centuries uroscopy came close to excluding all other types of medical observation. Constantine Africanus, who did much to spread Arabic medicine in medieval Europe, wrote that the "urine is better than the pulse to discover the disease from which the patient suffers," and Bernard Gordon declared, "the science of judging the urine is so easy that all can learn what they wish to know." The uroscopists were largely ignorant of both anatomy and therapeutics, yet it was a day when, apart from taking the patient's pulse and listening to his history, there was little that the physician could do in the way of diagnosis or therapy, and the water doctor or urine caster, or, as he was later called, the piss prophet,[1] with his elaborate gown and headdress, his mysterious urine glass, and his solemn mien, must have had a strong appeal for the sick, and possibly in some instances imparted to them some measure of psychosomatic benefit. Uroscopy was the degeneration of empirical observation into pure quackery, but for several centuries its charlatans traveled the country by horseback with only a urine glass slung on the arm, preying on the credulity and ignorance of the people. The urine caster served as the subject of almost every illustrious artist of the day, and one painter even portrayed Jesus in this role.

URINE AND ALCHEMY

It was not in the art of medicine, however, that urine was first to have a truly important part, but in the practical arts that supplied the foundations for the science of chemistry. Urine is a weak detergent by virtue of its urea content, and this detergent property is greatly enhanced when it is allowed to undergo bacterial fermentation, in consequence of which most or all of the urea is decomposed into the ammonium carbonate, a moderately alkaline salt. Such fermented urine has probably been used since time immemorial as a soap, but ancient literature bears no testimony on this point until the Roman period when it became the agent of choice for removing the fat and dirt from wool and for softening and bleaching the woolen fibers before dyeing. The Roman epigrammatist Martial inveighs against the nauseous smells emanating from the fullers' vats and relates that for this reason the police banished the guild to the far side of the Tiber. So important was urine in Roman industry that, according to Suetonius, the emperor placed a tax on such as was collected in public reservoirs. The use of fermented urine in fulling and crofting persisted until recent times, and by long tradition a genuine Highland homespun or Harris tweed is expected to carry the odor of the fermentation vat. (The odor generally comes from the use of surface water draining areas where sheep are pastured.) For centuries the herdsmen of Switzerland and Denmark used urine, a good source of potassium and nitrogen, as fertilizer, and among aboriginal peoples fermented urine has long been used in the tanning and softening of hides, for extracting dyes from various plants, and for mordanting other dyes in woolen fabrics. In relatively recent times it has been used to macerate tobacco leaves in the cigar industry and to flavor cheese.

The earliest alchemical interest in urine centers perhaps on the salts of ammonia, ammonium chloride and ammonium sulfate, collectively called "volatile salt" to distinguish them from nonvolatile salts such as sodium chloride. Pliny, in his "Natural History," refers to *Hammoniacus sal,* but how the Romans prepared sal ammoniac is unknown, though the name appears to have been derived from the fact that it was first made in the vicinity of the temple of Jupiter Ammon. The later alchemists prepared volatile salt for medicinal use by the dry distillation of fermented urine, and it came to play an important role in alchemical operations. In the 15th century Basil Valentine showed that a pungent volatile gas, free ammonia, was liberated from sal ammoniac by the action of alkalis, but it was not until 1777 that the Swedish chemist Scheele showed that ammonia contained nitrogen, and in 1785 Berthollet demonstrated that it was composed of nitrogen and hydrogen.

A more exciting substrate for alchemy was the element phosphorus. This word, in Latin meaning the morning star and in Greek a bringer of light, was early applied to any substance that glowed in the dark, and it was only after the 17th century that it was restricted to the element *phosphorus mirabilis* or *igeneus,* a waxy crystalline solid with a disagreeable odor that possessed the remarkable property of burning, when exposed to air, with a bright flame and great heat, for which reason it had to be prepared in the absence of air and stored under water. Pure phosphorus was first obtained by the alchemist Brandt of Hamburg in 1669, who started with microcosmic salt (ammonium sodium hydrogen orthophosphate), so named by the alchemists because it was obtained from the decomposing urine of man, the "microcosm"—an

1. Hart, J.: The Anatomie of Urines: Containing the conviction and condemnation of them; or the second part of our discourse of urines; detecting and unfolding the manifold falshoods and abuses committed by the vulgar sort of practitioners, in the judgement of diseases by the urines onely; together with a narrow survey of their substance, chiefe colours, and manifold contents, joyning withall the right use of urines; wherein is contained plentie of profitable and delectable histories concerning this subject; collected, as well out of the ancient Greeke, Latine, and Arabian authors, as out of our famous physitians of severall nations; their authorities quoted and translated out of the originall tongues, together with some of the authors owne observations. London, R. Mylbourne, 1625, p. 32. Now would I willing demand of the most cunning Pisse-prophet, what could he have found out by either of these urines?

ancient Babylonian antithesis opposed to the great world or "macrocosm" in which man lives. Though abundant in the earth and in all animals and plants, phosphorus is never found free in nature, and Brandt was able to sell the secret of its preparation to a man named Krafft who in 1677 exhibited some elementary phosphorus in England, where it attracted the attention of English chemists. In 1678 Kunckel and in 1680 Boyle worked out Brandt's secret of evaporating urine and dry-distilling the residue, collecting the distillate under water. Boyle communicated the method to a Mr. Hawkwitz, a druggist of London, who for more than 20 years prepared phosphorus from urine and sold it to all of the philosophers of Europe for a fancy price. Urine remained the sole source of this exciting element until Scheele in 1775 developed a method of preparing it from bones. But in 1801 Fourcroy was still able to recommend that urine might be an economical source of phosphorus in houses in which many persons lived and urine could be collected in troughs.

QUANTITATIVE STUDY OF URINE

It was in the 17th century that chemistry began to develop as a quantitative science. Alchemy had been a mixture of empiric observation with astrology, mysticism, and religious philosophy, and it had operated invariably in a cloak of secrecy and expressed itself in esoteric symbolism. Now the chemists, disregarding the stars and all transcendental implications, worked more or less openly and confined themselves to the composition and transmutation of what seemed to be the fundamental substances of nature. Urine was to supply much of the basic knowledge of the composition and transmutation of the substances of living animals.

The quantitative study of urine began in 1655 when van Helmont first determined its specific gravity by weighing it in a glass vessel with a narrow neck and known to hold a certain weight of rain water; he thus observed the dilute nature of the fluid excreted after the ingestion of water and the concentrated nature of that excreted after abstention from water and in fever, an observation that took much of the force out of the examination of random urine samples by the uroscopists. Bellini showed that changes in taste, color, and limpidity could be reproduced by careful evaporation and redilution with water, thus clearing the mystery of its variable composition, while the physiologist Haller quantitatively related the changes in concentration to the intake of water or fluid meals.

The alchemists had long used urine, sal ammoniac, or one or another of its derivative salts, in their search for the philosopher's stone, but the chemists were to put it to an alchemy of another sort. Before the end of the 18th century chemists had prepared from urine a variety of inorganic salts: sodium chloride, potassium chloride, ammonium chloride, ammonium phosphate, sodium phosphate, sodium acid phosphate, magnesium phosphate, sodium sulfate, calcium sulfate, calcium acid phosphate, triple phosphate of soda and ammonia (microcosmic salt), magnesium ammonium phosphate, and sodium dihydrogen phosphate—a notable list when one considers that few earthy substances had as yet yielded to analysis or chemical transformation.

It was generally known that the urine of man typically turned syrup of violets red, indicating the presence of an acid, whereas that of herbivorous animals turned this indicator blue or green, indicating an alkaline reaction, and now as the phosphatic salts came under examination attention was turned to variations in the acidity of the urine, laying the foundations for modern studies of acid-base balance.

Thomas Willis rediscovered the sweet taste of urine in diabetes mellitus, and recorded the fact in his great work on the brain (1664) (a volume illustrated by Sir Christopher Wren); a century passed before William Cruickshank, Dr. Johnson's personal physician, showed (1778) that the sugar in diabetic urine was not milk sugar, and another fifty years before Bonchardat and Peligot were able to identify it as glucose (1838). But after Claude Bernard's studies on glucosuria and liver glycogen, it became clear that glucose was the major fuel of the body, and it only remained for Minkowski's work on glucosuria in depancreatized dogs to initiate the modern era of carbohydrate metabolism.

Creatinine was discovered in human urine, allantoin in the fetal urine of the cow, and hippuric acid in the urine of horses and other herbivorous animals (Fourcroy and Vauquelin suggested that by hydrolysis of hippuric acid the urine of cattle could be made a profitable source of benzoic acid, which was formed by the hydrolysis of hippuric acid). The amino acids, leucine and tyrosine, were early isolated from urinary sediments, and cystine, along with the first-known purine bodies, xanthine and uric acid, was discovered in urinary calculi or bezoar stones. The term bezoar is a generic one denoting a variety of concretions found in the gastrointestinal or urinary tracts of mammals; first brought to Europe by the Arabs, bezoars became a universal antidote against disease, those of Oriental origin being most highly valued. It was to warn innocent persons against fake Oriental bezoars that Du Laurens, physician to Henry IV, coined the familiar phrase, "Beware of imitations." Since European color dealers dispensed their pigments in the urinary bladders of oxen and other animals, and the butchers, in preparing these bladders, came upon large numbers of these stones, the chemists had a good supply for their examination. Sydenham had first recognized the coincidence of urinary "gravel" in man with the painful swelling and concretions in the joints of persons suffering from gout, but Fourcroy was the first to give a reasoned account of the deposition of uric acid in the urinary tract and joints of the gouty victim and also the first to distinguish calcium oxalate and other types of urinary concretions from those formed by uric acid.

DISCOVERY OF UREA

Most important, however, was the discovery of urea. Von Rouelle first separated this compound from urine in an impure form in 1773, but a few years later Fourcroy and his colleague, Vauquelin, developed a quantitative method for its determination by precipitation as the nitrate salt, and showed that it was present in the urine of all animals that they studied. Fourcroy was the first to call it *urée*, and he speaks of it as "a most exalted animal matter . . . compounded by vital action." Here is epitomized the great division between the organic and the inorganic world. Alchemy and chemistry had long operated on mercury, potash, sal ammoniac, sulfur, quicklime, and, of course, on all the important metals,

such as gold, silver, tin, copper, and iron; but these substances were contained in rocks and earth devoid of life, whereas urea, like other compounds of animal or vegetable origin, was elaborated in the living organism by what was then a wholly mysterious vital force. Urea was the first such organic compound to be separated in a relatively pure state and to have its elementary composition determined in terms of the ammonia and carbon dioxide of which it is composed. It was the prize jewel of vitalism and organicism, until in 1828 Wöhler synthesized it from a simple solution of inorganic ammonium cyanate and the distinction between the organic and the inorganic kingdoms was relegated to the realm of rhetoric.

More scientific papers have probably been published on urea than on any other organic compound. Lavoisier had shown that the burning of the candle and of the mouse amount to much the same thing: fuel plus oxygen become carbon dioxide and ashes. As urinary glucose was to supply the key to the metabolism of carbohydrate, urea was to supply the key to the metabolism of protein and derivatively to the metabolism of fat. The mysteries of the warmth of the body, its muscular movements, its growth and all its related activities, had been pushed, so to speak, over the threshold of description.

COMMENT

The year 1801 saw the publication of Fourcroy's "System of Chemical Knowledge,"[2] a work that in the English translation (1804) ran to 11 large volumes. This was the first work of its kind, and almost one entire volume was devoted to the composition of urine. Whereas hitherto chemists had seen in this fluid an "attenuated oil, the ultimate products of the efforts of life and of the motion of the organs," Fourcroy speaks of it as neither a unity nor an end in itself: several different substances are evacuated at the same time, each presenting a particular advantage in its discharge. Thus Fourcroy adumbrates the role of the urine in the regulation of what, six decades later, Claude Bernard so aptly called our "internal environment." Add to the list of substances primarily discovered in the urine those that, discovered independently, have been isolated from the urine as normal metabolites—by rough count Neubauer and Huppert's "Analyse des Harns" (1910-1913) lists over 100 such organic compounds, and the list is possibly twice as large today—and one sees why the chemists have ever been more concerned with the composition of this liquid than with the search for the philosopher's stone: they early surmised that here indeed is a profitable approach to the study of the nature of man, the most intricate mechanism that exists on earth. May I say that in great measure man is what he is because his urine is what it is? And now that the story can be told of how man has evolved into his high estate, the elaboration of what Fourcroy would have called a "perfected urine" is seen to be the very foundation of this evolution. We can dismiss the philosopher's stone as a figment of the wishful imagination, but we cannot lightly dismiss the eloquent epitome written by Fourcroy in 1801:

> The urine of man is one of the animal matters that have been the most examined by chemists, and of which the examination has at the same time furnished the most singular discoveries to chemistry, and the most useful application to physiology, as well as the art of healing. This liquid, which commonly inspires men only with contempt and disgust, which is generally ranked amongst vile and repulsive matters, has become, in the hands of the chemists, a source of important discoveries, and is an object in the history of which we find the most singular disparity between the ideas which are generally formed of it in the world, and the valuable notion which the study of it affords to the physiologist, the physician, and the philosopher.

2. de Fourcroy, A. F.: Système des connaissances chimiques, et de leurs applications aux phénomènes de la nature et de l'art, Paris, Badouin, 1801, 11 volumes; translated by W. Nicholson, London, Cadell & Davis, 1804.

CLINICAL NOTES

BEDSIDE METHOD FOR JUDGING ANEMIA

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Anemia is a frequently missed clinical diagnosis; its severity too often is assumed to be a matter of conjecture. Nevertheless, the presence and intensity of anemia often can be suspected with fair accuracy by careful examination of the patient without recourse to complicated laboratory methods. In evaluating anemia at the bedside, the clinician examines particularly the skin, mucous membranes, conjunctiva, and fingernails. It is the purpose of this communication to direct attention to study of the creases of the palm as a simple clinical method for estimating the degree of pallor.

The hand as a source of clinical information is so obvious that it may be neglected.[1] The hand is richly endowed with blood vessels through which an enormous amount of blood flows. From time immemorial, the color of the palms and fingernail beds has been utilized for evaluating anemia. According to Wintrobe,[2] the palms are more reliable for judging pallor than the mucous membranes or conjunctiva. In studying the hand for evidence of pallor, the skin creases across the palm are often overlooked. These creases, or skin lines, differ anatomically and functionally from the surrounding skin that, at times, may be a deceptive index of anemia because of callous formation, pigmentation, or constitutional differences. It is not sufficiently appreciated that unless anemia is severe the skin creases across the palm normally retain a bright pink color. This reddish-pink color is constant regardless of how pale the intervening skin appears. According to Wintrobe,[3] when this red color is lost the hemoglobin level "may be judged as being below 7 grams per 100 ml."

To test the validity of a correlation of the coloring of the creases in the palms with the hemoglobin concentration, 1,500 patients from the services of the Staten Island

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Dr. Mary Trudeau assisted in this study.

1. Silverman, J. J., and Littman, D. S.: Cardiologist Looks at Hand, New England J. Med. **249**: 839, 1953.
2. Wintrobe, M. M.: Pallor and Anemia, in Harrison, T. R., and others: Principles of Internal Medicine, Philadelphia, the Blakiston Co., 1950, p. 253.
3. Wintrobe, M. M.: Clinical Hematology, ed. 3, Philadelphia, Lea & Febiger, 1951.

Hospital and from the hospital clinics were studied. For classification purposes the color of the creases was arbitrarily recorded as either "present" or "absent." In doubtful or borderline instances, the color was recorded as "absent." To accentuate the color contrast, the palm of each patient was forcibly stretched, with the fingers extended. This is facilitated by the opposing thumbs of the examiner (figure). By use of this technique, the distinctive reddish-pink color of the crease in the palm is unmistakable. For comparative purposes, the examiner's own palm served as a control. A hemoglobin determination of each patient was obtained, utilizing either the Sahli or photoelectric method. Notation of the color was made in each instance without knowledge of the patient's hemoglobin level. The results are listed in the table. There were 1,454 patients with a hemoglobin value above 7 gm. per 100 ml., and in 1,438 of these the color of the creases was "present." There were 46 patients whose hemoglobin level measured less than 7 gm. per 100 ml., and in 42 of this group an absence of the normal red color in the creases was noted.

Correlation of Hemoglobin Values with Color of Palmar Creases in 1,500 Patients

Hemoglobin (Gm./100 Ml.)	Total No. of Patients	Presence of Color (No. of Patients)	Absence of Color (No. of Patients)
3.0- 3.9	2	0	2
4.0- 4.9	8	0	8
5.0- 5.9	12	1	11
6.0- 6.9	24	3	21
7.0- 7.9	20	18	2
8.0- 8.9	25	19	6
9.0- 9.9	33	30	3
10.0-10.9	32	30	2
11.0-11.9	63	62	1
12.0-12.9	181	180	1
13.0-13.9	320	319	1
14.0-14.9	390	390	0
15.0-15.9	304	304	0
16.0-16.9	62	62	0
17.0-17.9	19	19	0
18.0-18.9	1	1	0
19.0-19.9	2	2	0
20.0-20.9	2	2	0

The thumbs of the examiner are forcibly opposed to the palm of the patient so that the palm is stretched and the palmar lines can be seen clearly.

It is apparent that the color of the palmar creases is a convenient, practical guide for judging severe pallor, and for clinical purposes it is remarkably accurate. Despite the multitude of technical advances achieved up to the present time, it is still pertinent to emphasize bedside methods requiring only simple observation and no special equipment.[1] It is realized that the method proposed for evaluating pallor is a subjective one and, therefore, that it is prone to error. Nevertheless, by following the technique described, which requires little effort and experience, the normal bright pink color of the palmar crease is easily identified. When this color is lost, the hemoglobin level is likely to be below 7 gm. per 100 ml. In this study of 1,500 patients only 20 failed to show this correlation.

100 Central Ave. (1).

TREATMENT OF AMEBIASIS WITH FUMAGILLIN

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In his article, "The Use of Fumagillin in Amebiasis," Anderson [1] has pointed out that in 1949, Hanson and Eble [2] isolated from Aspergillus fumigatus a crystalline substance consisting exclusively of carbon, hydrogen, and oxygen, and which they named fumagillin. McCowen, Callender, and Lawlis [3] demonstrated the direct amebacidal effect of this substance. In vitro, in the absence of multiplying bacterial associates, fumagillin was active against Endamoeba histolytica in a dilution of 1:400,000. Hrenoff and Nakamura [4] demonstrated that in the presence of Trypanosoma cruzi, the amebacide effect of fumagillin is still present in a dilution of 10 to 15 million. In 1952, Anderson and Nakamura [5] showed that the effect of fumagillin is due to a complete inhibition of the metabolic activity of E. histolytica. The first observations made with fumagillin in animals and in man suffering from amebiasis were promising.

As yet, very few clinical observations are found in the literature. The following three cases may be of interest, as they show the results and the side-effects of fumagillin.

REPORT OF CASES

CASE 1.—A 60-year-old man had acute gastroenteritis. Temporarily, symptomatic treatment was effective. The gastroenteritic symptoms reappeared, accompanied by alternating diarrhea and constipation. Examination of the stools showed numerous trophozoites and cysts of E. histolytica. Although the patient had lived for many years in Israel, where gastrointestinal infections are endemic, he did not state that he had had any of them before.

In this case treatment was based exclusively on fumagillin. The patient received 10 mg. three times a day for 3 days and

1. Anderson, H. H.: The Use of Fumagillin in Amoebiasis, Ann. New York, Acad. Sc. **55**: 1118, 1952.
2. Eble, T. E., and Hanson, F. R.: Fumagillin, Antibiotic from Aspergillus Fumigatus H-3, Antibiotics & Chemother. **1**: 54, 1951.
3. McCowen, M. C.; Callender, M. E., and Lawlis, J. F., Jr.: Fumagillin (H-3), New Antibiotic with Amebicidal Properties, Science **113**: 202, 1951.
4. Hrenoff, A. K., and Nakamura, M.: In Vitro and in Vivo Studies of New Antibiotic, Fumagillin, with Endamoeba Histolytica, Proc. Soc. Exper. Biol. & Med. **77**: 162, 1951.
5. Anderson, H. H., and Nakamura, M.: Drug Effects on the Metabolism of Endamoeba Histolytica; abstracted, Fed. Proc. **11**: 378, 1952.

20 mg. three times a day for 7 days, i. e., a total of 510 mg. of fumagillin during 10 days.

Stools were examined (each time by the same examiner) on the 3rd, 5th, 7th, and 11th days. After three days the stools were already free of amebas; neither trophozoites nor cysts were found by direct examination or in a culture. Urine examination showed a slight albuminuria at the beginning, which did not change significantly in the course of treatment. The blood chemistry studies showed normal results at the beginning of the treatment as well as 14 days after the end of treatment.

The drug was well tolerated, although headaches were noted during the course of treatment. Occasionally the patient complained of nausea, but did not vomit. Four weeks after the end of treatment the patient noticed peeling of palms and soles, which persisted for about two weeks and disappeared without any therapy. At the same time a right hydrocele developed. There were no clinical signs of an acute inflammation, though the patient complained of a disagreeable tenderness. After two weeks the hydrocele reached the size of a medium-sized apple. Puncture showed a fluid, which was sterile, containing lymphocytes and histiocytes.

Five months after the beginning of treatment the patient's general condition is good, and he is free of any symptoms. No E. histolytica can be found in the stools.

Case 2.—A 39-year-old woman had suffered from chronic recurrent amebiasis for many years. She had another relapse consisting of diarrheal stools with mucus and blood and amebic hepatitis. The principal complaints were pains in the right hypochondrium, diarrhea, subfebrile temperature, and subclinical icterus. Examination showed an enlarged liver two fingerbreadths below the right lower rib and secondary anemia. In the urine a few leukocytes were seen. In the stools, trophozoites and cysts of E. histolytica were found. The patient was treated exclusively with fumagillin. She was given 10 mg. three times a day for 3 days and 20 mg. three times a day for 8 days, i. e., 570 mg. in 11 days.

In the first days the medication was well tolerated. From the third day on there was pronounced anorexia with occasional vomiting. At the same time the patient complained of nausea and of a peculiar loss of sensation in hands and feet, which appeared some 30 to 40 minutes after she had taken the capsules and which persisted for about 20 minutes. She also had difficulty in hearing, which she described as "hearing through cotton wool." There was a painful burning sensation in the eyes. On the fifth day of treatment, the patient began to suffer from strong headaches at the occiput and persisting nausea, as well as diarrhea alternating with constipation. Occasionally the headaches alternated with vertigo. Periods of voracious appetite were reported as a particularly striking symptom. On the 12th day after the beginning of treatment there appeared pains in the right thigh, together with swelling and local tenderness, so that thrombophlebitis was suspected. At the same time a generalized folliculitis developed in the patient's face.

Three weeks after the beginning of treatment a shedding of the upper epithelial layer of the palms began and persisted for about two weeks. No modification of the blood picture or of the urine was observed in the course of treatment.

The patient insisted on continuing treatment despite the extremely disagreeable side effects, so that she would get rid of the amebas. The stools were examined for E. histolytica on the 3rd, 5th, 7th, 9th, and 11th day of treatment. The patient and the examiner were both astonished when, on the third day of treatment, the stools were free of amebas for the first time in many years. During the 14 weeks after the end of the treatment, further examinations were made. All of them showed normal results. At present the patient feels well, has gained in weight, and has no more symptoms.

Case 3.—A 43-year-old woman had chronic entamebiasis. For the last two months she had repeatedly had diarrheal stools containing blood and mucus. During that time she had lost 5 kg. in weight. She tolerated very few foods and suffered from marked tenesmus. The mucosa of the mouth showed signs of a heavy vitamin B deficiency. There was a macrocytic anemia. Albuminuria and the presence of many leukocytes in the urinary sediment were shown by urinalysis. In the stools there were E. histolytica (trophozoites), Endamoeba coli, and Trichomonas hominis. There was also monilial vaginitis.

The patient was treated with fumagillin, starting with 10 mg. three times a day. On the first day of treatment the patient complained of strong headaches and nausea. The diarrhea stopped, and a painful constipation appeared. On the third day the patient refused to take any further capsules of fumagillin because of unbearable headaches. On that day she had a fever, and tonsillitis with swelling of the cervical lymph nodes developed. The tonsillitis was treated with sulfadiazine, and the patient's throat healed without complications. After an interruption of four days, treatment was restarted with 10 mg. of fumagillin two times daily. Although headaches appeared again, the nausea was less than before and the patient continued to take the capsules. The very obstinate constipation reappeared. Treatment was continued for another 10 days with 20 mg. of fumagillin per day. Stomach aches of short duration appeared frequently after meals. The anemia did not change in the course of treatment. The urine became normal. Menstruation was delayed for two weeks. The possibility of a pregnancy was excluded by a negative Aschheim-Zondek test.

Examinations of the stools were made on the 3rd, 5th, 9th, and 16th day after the beginning of treatment. None of them revealed E. histolytica or E. coli, while T. hominis was constantly present.

Four months after the beginning of treatment there are still slight intestinal disturbances, a tendency towards spasms, and tenderness of the ascending colon and of the region of the bile vesicle. A roentgenologic examination did not show any pathological changes in the gastrointestinal tract. The tendency to constipation persists. E. histolytica is not present in the stools.

The few observations found in the literature concerning the treatment of amebiasis by fumagillin unanimously stress the very high amebacidal effect of this antibiotic. Oliver-Gonzalez and others [6] report 28 cases in which 10 to 30 mg. of fumagillin per day was given during 10 days. As in the cases described above, the stools were usually free of amebas after three to five days. Little is said in the report about the side-effects. Some patients had transient anorexia and headaches during the first three days. A patient in whom pruritus ani and muscular pains developed was shown to be hypersensitive to streptomycin and penicillin.

McHardy and others [7] communicate that the appearance of side-effects seems to be directly related to the daily dose of fumagillin. They describe the reactions of 10 students who were given at first 10 mg. and later up to 100 mg. of fumagillin per day. Thirty milligrams per day caused anorexia, 60 mg. nausea and vertigo, 70 mg. transient diarrhea, and 90 mg. per day vomiting. Out of a total of 60 patients treated by McHardy, 18 could be controlled during a long time. Three of them showed relapses after 4, 6, and 18 months respectively.

Armstrong,[8] who observed 20 cases, reports success in 85% of cases. However, he finds fumagillin less effective than chlortetracycline (Aureomycin). Moreover, he reports that four of the patients successfully treated by him had relapses after two months.

6. Oliver-Gonzalez, J., and Dobal, J. M.: Treatment of Endamoeba Histolytica Infections in Man with Fumagillin, Bol. Assoc. Méd. Puerto Rico **45**: 127, 1953.

7. McHardy, G.; Bechtold, J. E.; Welch, G. E., and Browne, D. C.: Fumagillin as an Amebacide, South. M. J. **46**: 428, 1953.

8. Armstrong, T. G.: Recent Experiences in Treatment of Amoebiasis, South African M. J. **27**: 42, 1953.

SUMMARY

In the three cases described (a fourth case has been omitted because no follow-up was possible), fumagillin proved to be a very effective amebacidal drug; however, it causes a series of undesirable side-effects of surprising and bizarre forms. Whether these side-effects can be avoided by smaller doses will only be shown by observation of a larger number of patients. Particularly striking side-effects were peeling of the skin of the palms and soles in two of three cases, beginning in both cases three to four weeks after the start of treatment; the appearance of a hydrocele in one case, and peculiar sensory disturbances in the hands and feet and irregularities of hearing in one case.

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SCLEREMA NEONATORUM TREATED WITH CORTICOTROPIN (ACTH)

REPORT OF TWO CASES

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Harold A. Aaron, M.D.
and
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Sclerema neonatorum [1] is a peculiar induration of the skin and subcutaneous tissue that often starts in the buttocks and thighs and involves the remainder of the legs, the trunk, the arms, and the face. The soles, the palms, and the genitalia are spared. It is found in premature infants or in very young infants suffering from congenital debility, diarrheal conditions, dehydration, and circulatory stasis. There is associated marked lowering of body temperature; the skin is stiff, cold, and often mottled as in peripheral circulatory failure; and there is interference with activity, respiration, and sucking. When it appears, it is of very serious prognostic importance despite the fact that these infants have been treated for the primary disturbances such as dehydration, shock, and acidosis. Until recently, about 75% of the infants treated died. Reports of the successful treatment of sclerema neonatorum with corticotropin (ACTH) and cortisone in addition to the basic treatment have appeared.[2] Following is a report of two additional recoveries with the aid of corticosteroids.

From the pediatric services of Harlem Hospital and Lebanon Hospital.

1. Finkelstein, H., and Sommerfeld, P.: Pathogenesis of Sclerema in Infants, Monatschr. f. Kinderh. **25**: 105 (March) 1923. Hamburger, H. J.: Case of Sclerema Neonatorum, Indian J. Pediat. **5**: 246 (Oct.) 1938. Gray, A. M. H.: On Identity of Adiponecrosis Subcutanea Neonatorum with Sclerema Neonatorum, Brit. J. Dermat. **45**: 498 (Dec.) 1933. Hughes, W. E., and Hammond, M. L.: Sclerema Neonatorum, J. Pediat. **32**: 676 (June) 1948. Simpson, C. K.: Sclerema Neonatorum (Adiposum), Guy's Hosp. Rep. **84**: 307 (July) 1934. Brain, R. T.: Sclerema Neonatorum, Proc. Roy. Soc. Med. **46**: 543 (July) 1953. Skeer, J.: Sclerema Neonatorum: Report of Cure by X-Ray Therapy, Arch. Dermat. & Syph. **19**: 732 (May) 1929.

2. Kendall, N., and Ledis, S.: Sclerema Neonatorum Successfully Treated with Corticotropin (ACTH), A. M. A. Am. J. Dis. Child. **83**: 52 (Jan.) 1952. Grotts, B. F.: Sclerema Neonatorum: Report of Case, Arch. Pediat. **68**: 585 (Dec.) 1951. Kendig, E. L., Jr., and Toone, E. C., Jr.: Cortisone in Treatment of Sclerema Neonatorum, A. M. A. Am. J. Dis. Child. **81**: 771 (June) 1951.

CASE 1.—A 6-week-old Negro male infant was admitted to the Pediatric Service May 2, 1953, because of severe diarrhea and dehydration. The mother was 28 years old, seronegative, Rh positive, and in good health. Her other children were in good health. Labor had been normal and delivery was spontaneous. The birth weight was 9 lb. (4,082 gm.). The neonatal progress was uneventful. The infant was placed on an evaporated milk formula with cane sugar, which was well tolerated.

The baby was well until three days prior to admission, at which time diarrhea appeared and there were six loose, green stools on the first day. The following day, the stools increased in number to 10 a day and became watery in consistency. The diarrhea continued and the infant was admitted to the hospital on the third day of illness.

On admission, the infant appeared acutely ill, dehydrated, and with evidence of loss of weight. There was a moderate loss of skin turgor. The anterior fontanel was depressed. At this time there was no evidence of sclerema. Examination of the ear, nose, and throat showed essentially normal structures. A neurological examination revealed no abnormalities.

The blood cell count showed red blood cells, 3,090,000; leukocytes, 16,150; polymorphonuclear cells, 71%; lymphocytes, 23%. The hemoglobin level was 8 gm. per 100 cc. A stool culture failed to reveal any intestinal pathogens. The urine showed no abnormalities. The blood carbon dioxide combining power was 16 vol. %. The urea nitrogen level was 20 mg. per 100 cc.; creatinine, 0.8 mg. per 100 cc.; sugar, 120 mg. per 100 cc.; serum albumin, 1.95 gm. per 100 cc.; globulin, 1.45 gm. per 100 cc.; albumin/globulin ratio, 1:34; and total protein, 3.40 gm. per 100 cc. Roentgenograms of the chest and lung bones were within normal limits.

During the first two days of hospitalization, the condition remained unchanged. The diarrhea was still severe, but the hydration of the infant improved with subcutaneous administration of 5% dextrose in distilled water and lactated Ringer's solution. The acidosis was less marked; blood carbon dioxide combining power was now 32 vol. %. On the fourth hospital day, hardening of the subcutaneous tissues of the legs, buttocks, and lower trunk became evident. This peculiar ligneous quality of the subcutaneous tissues now extended upward to the arms. The entire body became rigid. Temperature at this time was subnormal (97.5 F). It was impossible to elevate the skin by pinching or to separate it from the subcutaneous tissue.

On the fifth hospital day, 5 mg. of corticotropin (ACTH) was administered parenterally, this dose being repeated at intervals of six hours for a total of 12 doses. The clinical response was dramatic. After two days of corticotropin therapy the hardening of the tissue began to disappear, and it had completely regressed six days after discontinuance of the corticotropin therapy. The diarrheal condition continued unabated through the sclerematous period, and was finally controlled by supportive therapy and administration of protein milk. The patient was discharged on July 13, 1953, weighing 10 lb. 2 oz. (4,591 gm.) and in good condition.

CASE 2.—A female infant had been born prematurely Aug. 13, 1953, at 31 weeks' gestation. She was born by spontaneous vertex delivery and weighed 2 lb. 5 oz. (1,048 gm.). There was a history of premature separation of the placenta. The infant's color and cry were good, and no gross abnormalities were noted. The infant was kept in an Isolette, and oxygen was administered. Feedings of 5% lactose in water were given by dropper after 48 hours and after another 12 hours, a formula of skim milk powder (Alacta) with added carbohydrate was given by gavage.

On the third day, stiffness of the skin and subcutaneous tissues of the buttocks and cheeks were noted. The cry was weak, and the infant failed to suck. There was no cyanosis, and the body temperature was 97 F. There was also some stiffness of the legs and thighs, and respirations were shallow. The next day the hardening became more pronounced; it involved the arms and back including the posterior chest wall. The color was fairly good but the cry was very weak. There had been meconium stools and a satisfactory urinary output. Hypodermoclysis of 5% dextrose with lactated Ringer's solution was given every eight hours. The prognosis, at this point, was considered to be hopeless. Corticotropin therapy was started, with 3 mg. given

intramuscularly every eight hours. There was little change the next day, but after 48 hours of the hormone therapy, the infant showed remarkable improvement. The scleremalous involvement was now much less pronounced, and the infant's general condition appeared much better. The hardening of the skin rapidly continued to diminish, and by the sixth day the skin had completely returned to normal. Corticotropin was discontinued after four days of therapy. The total amount administered was 30 mg. The general condition of the child continued to show rapid progress. The hypodermoclysis was discontinued, the gavage feedings were increased, and the infant continued to gain weight. In the supportive therapy were included the administration of multivitamin preparations, ascorbic acid, blood transfusion, and iron. The discharge weight on the 58th hospital day was 5 lb. 2 oz. (2,323 gm.).

COMMENT

The cause or exact nature of the pathological process in sclerema neonatorum is not clearly understood. Histological study has revealed only thickening of connective tissue bands. The different composition of infant fat may predispose to hardening under conditions of circulatory stasis or may be related to its low iodine number and its high melting point. The arguments in support or opposition have been dealt with in literature, but all observers are in agreement that treatment insuring the proper intake and utilization of fluids and electrolytes is necessary to secure reversal of this condition. Corticotropin and cortisone may act in this way, although the suppression of formation of fibroelastic and connective tissue may play a part. When recovery takes place, it is complete.

SUMMARY

Two patients with sclerema neonatorum, one a newborn infant with severe diarrhea, dehydration, and acidosis, and the other a very small premature infant weighing 2 lb. 5 oz. (1,048 gm.), were treated with corticotropin (ACTH) with prompt cessation of the progression of the disease and rapid reversal to normal.

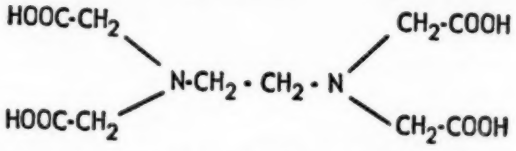
15 W. 81st St. (24) (Dr. Eisenoff).

Pheochromocytoma.—Every pheochromocytoma must be regarded as potentially malignant. Therefore, there is a double responsibility and an urgent need to diagnose this completely curable disease early. The alarm is sounded early in many cases, for the intermittent discharge of epinephrine secreted by some pheochromocytomas produces readily recognizable paroxysms of palpitation, headaches and apprehension. Even without paroxysms, hyperepinephrinemia produces hypermetabolism in the presence of a normal radioactive iodine uptake. Epinephrine is diabetogenic, and in many instances the blood and urine studies suggest diabetes mellitus. Pheochromocytoma may produce a picture of paroxysmal nephritis. A more recent clinical clue has been the description of the frequent association af neurocutaneous diseases with pheochromocytoma. The norepinephrine component of pheochromocytoma's secretion is responsible for the systolic and diastolic hypertension which may be paroxysmal or malignant, but most often is sustained. Since such hypertension is often asymptomatic, pharmacologic tests are obligatory in unmasking the true etiology. Regitine is readily applicable for office use, and it serves admirably as a screening procedure. After a positive Regitine test and in other suspected cases, the patient must be studied in a hospital environment. Confirmatory pharmacologic tests must be performed, since at this time there is no single foolproof test available for the diagnosis of pheochromocytoma.—A. Soffer, M.D., Office Diagnosis of Pheochromocytoma, *Postgraduate Medicine*, March, 1954.

TREATMENT OF LEAD POISONING BY CHELATION

Lawrence H. Cotter, M.D., New York

Chelating agents have been used in industry [1] for some time. The substance under consideration here, ethylene diamine tetra-acetic acid,[2] with the structural formula shown in the figure, has proved valuable for recovering trace metals from foods and beverages and rare metals in analyzing solutions. Pathologists find it useful in decalcifying bone,[3] and Gellhorn [4] and others have used it clinically in reducing hypercalcemia. The effects of the



calcium chelate on the excretion and storage of lead were studied by Rubin [5] in his experiments on rabbits. Many other animal studies have been reported, and it is in fairly general use by veterinarians.[6] Bessman, Reid, and Rubin[7] reported a case in 1952 in which lead encephalopathy in a human being was successfully treated by the intravenous injection of calcium disodium versenate. The same year Belknap [8] obtained excellent results in three cases with the same treatment. Popovici and associates [9] found that the chelating agent was absorbed through the skin in human beings with resultant diminution of the serum calcium. The practicability of oral administration was, therefore, established, but there remained the danger of eliminating the normal plasma electrolytes coincidentally with the lead. The recent development of a disodium calcium salt of the amino acid (Versene) made treatment possible without this disadvantage. It further proved to be pleasant to take, whereas all patients had complained of the persistent nauseating taste of the acid. The method employed in this series was to give a test dose of 250 mg. of Versene by mouth. If no allergic symptoms were observed at the end of 24 hours, the initial dose was repeated every 2 hours during the day until a total of 2 gm. had been given. This was continued for a week, by which time the patient had received 14 gm. There were no complaints, and most of the patients volunteered the information that they felt an urge to urinate about 15 minutes after taking the pills.

From the Department of Medicine, Columbia University, College of Physicians and Surgeons, and Presbyterian Hospital.

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2. Pharmacology, Physiology, Biochemistry and Toxicity of Versenes, Framingham, Mass., Bersworth Chemical Co., Sept. 19, 1952.

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7. Bessman, S. P.; Reid, H., and Rubin, M.: Treatment of Lead Encephalopathy with Calcium Disodium Versenate: Report of Case, M. Ann. District of Columbia **21**: 312, 1952.

8. Belknap, E. L.: EDTA in Treatment of Lead Poisoning, Indust. Med. **21**: 305, 1952.

9. Popovici, A.; Geschickter, C. F.; Reinovsky, A., and Rubin, M.: Experimental Control of Serum Calcium Levels in Vivo, Proc. Soc. Exper. Biol. & Med. **74**: 415, 1950.

Before the routine of treatment was started, a careful biochemical record was made, including blood cell count, reticulocyte count, routine urinalysis, erythrocyte sedimentation rate, blood sugar, serum nonprotein nitrogen, uric acid, proteins, alkaline phosphatase, total and free cholesterol, and carbon dioxide content, as well as determination of the blood content of calcium, copper, sodium, total halogen and lead, and urine lead. For the sake of brevity only those determinations that were abnormal are given in the case reports. These tests were, however, done completely before medication was begun and a month after administration of the drug was stopped. Seven of the patients have been under observation for at least two years. The case reports below have been selected from those of a series of 26 patients as typical of the exposure, symptoms, and recovery of the group.

REPORT OF CASES

CASE 1.—A 40-year-old Argentine painter had spent all his working life brushing and spraying paint. For the last two years he had been employed scraping and painting steel bridges. He gave a history of vomiting, cramps, and weakness of three weeks' duration. On physical examination he was noted to be a powerfully built man in acute distress. He showed tenderness and rigidity over the whole abdomen, with diminution of sensation and tingling on both lower extremities and hands and tenderness over the calf and biceps muscles. He had the typical "high-stepping" gait. Blood chemistry studies showed hemoglobulin level, 14 gm. per 100 cc., red blood cells, 3,500,000, and white blood cells 5,600 per cubic millimeter, with neutrophils 51%, monocytes 3%, lymphocytes 41%, eosinophils 3%, basophils 2%, and reticulocytes 0.6%. The patient was given the previously outlined dosage of Versene. He said he felt better on the second day, lost his pain, and regained his appetite. A month later he was symptom-free. At this time, the hemoglobin level was 16 gm.; red blood cells, 4,800,000; and white blood cells, 6,300, with neutrophils 61%, monocytes 2%, lymphocytes 28%, eosinophils 7%, basophils 2%, reticulocytes 2.5%. Chemical findings are given in the table.

CASE 2.—A 25-year-old white painter came to Vanderbilt Clinic with a history of joint pains, nausea, and severe fatigue of four weeks' duration. He had used a considerable quantity of red lead and had recently been subjected to continuous dust while wire-brushing old painted steel. On physical examination, he showed marked pallor, pyorrhea, and a definite lead line; there was tenderness in the right upper quadrant. Blood chemistry studies showed a hemoglobin level of 9.1%; erythrocytes, 2,800,000 per cubic millimeter; and white blood cell count, 7,600, with neutrophils 65%, lymphocytes 10%, monocytes 2%, and eosinophils 23%. Basophilic stippling was observed. The erythrocyte sedimentation rate was 18 mm. per hour. The urine showed a trace of albumin with an occasional white blood cell and hyaline casts. The man was seen one week after treatment was started, at which time the lead line and pyorrhea had disappeared. He said he had an urge to urinate after taking every pill and that his weakness was improving rapidly. He had no tenderness. At this time the hemoglobin level was 12.5 gm.; red blood cell count, 3,400,000; and white blood cell count 8,600, with neutrophils 73%, lymphocytes 20%, monocytes 5%, and eosinophils 2%. The red blood cells showed polychromatophilia and basophilic stippling, and there was an occasional nucleated cell. Chemical findings are given in the table. This case was typical of the group in which patients show a lead line and a high eosinophil count. In every case in which the blood picture returned to normal and the line vanished, the pyorrhea also disappeared; this suggests that the latter is a secondary condition.

CASE 3.—A 26-year-old Puerto Rican, engaged in burning paint, gave a history of pain in the abdomen for a year and progressive weight loss of 10 lb. (4.5 kg.). He had undergone fluoroscopy and had been treated for a gastric ulcer. Blood chemistry studies showed a hemoglobin level of 13 gm.; red blood cell count, 2,800,000; and white blood cell count, 5,000, with neutrophils 71%, monocytes 3%, lymphocytes 23%, eosinophils 2%, basophils 1%, and reticulocytes 2%. Immediately after starting treatment he became symptom-free and went back to work. When he was examined after discontinuing treatment, he was discharging stored lead, with a rise in the amount quantitated in both blood and urine. However, he felt so well that no further medication was indicated, and at the end of a month he no longer excreted lead. The final blood chemistry studies showed a hemoglobin level of 14 gm.; red blood cell count, 3,500,000; and white blood cell count, 5,000, with neutrophils 60%, lymphocytes 24%, monocytes 2%, eosinophils 14%, and reticulocytes 1.4%.

CASE 4.—A 23-year-old Greek went to work as a painter at the age of 17. He had recently been engaged in brushing and scraping painted steel and in using red lead. He gave a history of abdominal pain, progressive loss of weight now amounting to 5 lb. (2.3 kg.), and headache for three months. Examination showed a thin, pale, young man in acute discomfort, with tenderness and rigidity of the abdomen. The hemoglobin level was 10.3 gm.; erythrocyte count was 3,300,000 per cubic millimeter; and white blood cell count was 5,800, with neutrophils 71%, lymphocytes 20%, monocytes 6%, eosinophils 2%, basophils 1%, and reticulocytes 0.3%. The red blood cells varied in size, shape, and pigmentation, and basophilic stippling was present. After routine dosage with Versene, the man said he felt perfectly well and returned to work. On reexamination his hemoglobin level was 12.5 gm.; red blood cell count, 4 million; and white blood cell count, 6,000, with neutrophils 70%, lymphocytes 22%, monocytes 6%, eosinophils 1%, and basophils 1%. The red blood cells were normal in appearance with no stippling.

Chemical Data on Patients Treated by Chelation

	Case 1		Case 2		Case 3			Case 4	
						After Treatment			
	Before Treatment	After Treatment (1 Week)	Before Treatment	After Treatment (1 Week)	Before Treatment	(1 Week)	(1 Mo.)	Before Treatment	After Treatment (1 Week)
Serum Cholesterol									
Total cholesterol (mg. per 100 cc.)	132	144	126	154	96	105	153	150	150
Free cholesterol (mg. per 100 cc.)	40	60	48	40	40	40	51	...	...
Combined cholesterol (mg. per 100 cc.)	92	84	82	114	56	65	102	...	...
Blood lead (10^{-2} mEq./L.)	3.3	0	1.1	0.85	1.3	2.1	0	2.1	0
Urine lead (10^{-2} mEq./L.)	0.06	0	0.05	0.14	0.02	0.84	0	0.005	0
Serum Electrolytes									
Copper (10^{-3} mEq./L.)	2.2	1.9	5.9	5.6	12.5	1.6	1.6	1.25	0.9
Sodium (mEq./L.)	133.0	135	134	141	134	140	141	127	141
Calcium (mEq./L.)	4.5	4.5	4.5	4.1	4.9	4.6	4.8	5.0	4.9
Magnesium (mEq./L.)	2.4	1.9	5.0	3.8	2.5	2.7	2.1	2.6	2.5
Phosphorus (mEq./L.)	3.5	4.0	5.6	6.2	3.5	11.3	4.5	...	...

COMMENT

The question of safety is paramount in testing any new drug. In the case of disodium calcium ethylene diamine tetra-acetate, there was a known affinity for the plasma

electrolytes. The significance of the table is that the calcium, copper, sodium, and magnesium content was at no time seriously disturbed. Two patients in the series showed a rise in total serum inorganic phosphate, and two showed a rise in serum copper. The serum cholesterol was low in the average case and was the slowest factor to return to normal. In the determination of all the chemical values, muffle furnace methods are required to destroy the chelating agent.

620 W. 168th St. (32).

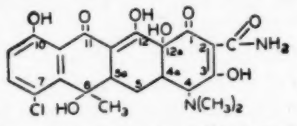
COUNCIL ON PHARMACY AND CHEMISTRY

NEW AND NONOFFICIAL REMEDIES

The following additional articles have been accepted as conforming to the rules of the Council on Pharmacy and Chemistry of the American Medical Association for inclusion in New and Nonofficial Remedies. A copy of the rules on which the Council bases its action will be sent on application.

R. T. STORMONT, M.D., *Secretary.*

Aureomycin Calcium.—The calcium salt of 7-chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide. It complies with the requirements of the Federal Food and Drug Administration. The exact chemical formula of aureomycin calcium is unknown. It is believed that two of three acid hydrogens of aureomycin are replaced by calcium. The structural formula of aureomycin may be represented as follows:



Actions and Uses.—Aureomycin calcium has the same actions and uses as the hydrochloride salt. See New and Nonofficial Remedies under the monograph on aureomycin hydrochloride. The calcium salt is useful for oral administration of the antibiotic in concentrated form for patients who cannot take dry forms of the drug.

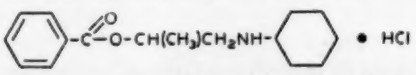
Dosage.—Aureomycin calcium is administered orally in the form of drops for infants and in the form of syrup for children or adults who do not readily take dry forms of the drug. The dosage for the calcium salt is expressed in terms of the hydrochloride salt.

Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

Oral Drops Aureomycin Calcium: 10 cc. and 20 cc. dropper bottles. A suspension containing 100 mg. of aureomycin calcium in each cubic centimeter. Preserved with 0.08% methylparaben and 0.02% propylparaben.

Syrup Aureomycin Calcium: 118 cc. and 473 cc. bottles. A syrup containing 31 mg. of aureomycin calcium in each cubic centimeter. Preserved with 0.08% methylparaben and 0.02% propylparaben.

Hexylcaine Hydrochloride.—Cyclaine Hydrochloride (Sharp & Dohme).—$C_{18}H_{28}NO_2.HCl$.—M.W. 297.82.—1-Cyclohexylamino-2-propyl benzoate hydrochloride.—The structural formula of hexylcaine hydrochloride may be represented as follows:



Actions and Uses.—Hexylcaine hydrochloride is a soluble local anesthetic suitable for infiltration, spinal (subarachnoid) anesthesia, surface (topical) anesthesia, and nerve block, including caudal (extradural sacral) block and lumbar epidural block. Animal experiments indicate that the onset of its anesthetic effect is rapid and that, from the standpoint of duration of anesthesia and degree of motor paralysis produced, it compares favorably with equal concentrations of the more active local anesthetic compounds in use. When applied topically, it is at least as potent as equal concentrations of cocaine. Clinical studies also indicate that, when used for infiltration and nerve block, it is faster and longer acting than an equal concentration of procaine.

Hexylcaine hydrochloride shares the toxic potentialities of other local anesthetic agents and should be employed with the same precautions and in accordance with established techniques of administration.

Dosage.—Hexylcaine hydrochloride should be administered in the smallest dose that will give the required anesthesia.

For infiltration anesthesia to relieve local pain, 5 to 65 cc. of a 1% solution is injected into the affected areas; up to 90 cc. of the same concentration may be required for surgical procedures. More dilute solutions may be used with a corresponding increase in the volume to be injected. For most nerve blocks, 2 to 10 cc. of a 1% solution is recommended. For single-injection caudal (extradural sacral) block, the dose is 25 to 35 cc. of a 1% solution; for continuous caudal block, 20 to 50 cc.; and for lumbar epidural block, 25 to 50 cc.

For single-dose spinal anesthesia the amount to be injected is 15 to 50 mg. administered by diluting 0.6 to 2 cc. of a 2.5% solution containing 10% dextrose with 0.3 to 2 cc. of aspirated spinal fluid, depending on the final hyperbaric concentration of dextrose desired, the site and type of surgical operation, and the condition of the patient. A total volume (after appropriate dilution) of 4 cc. is usually employed for operations above the level of the umbilicus and a total of 1 to 3 cc. for surgery below that level. The position of the patient is altered to achieve the exact level of anesthesia desired. For low spinal anesthesia of obstetric patients during delivery, a dose of 20 to 25 mg. (0.8 to 1 cc. of the 2.5% solution) is injected without barbotage at the third or fourth lumbar interspace and the position of the patient regulated to obtain anesthesia extending to a level of 5 to 9 cm. below the umbilicus. For cesarean section, 25 mg. is usually employed and the patient positioned to obtain anesthesia to the level of the umbilicus. For fractional spinal anesthesia, an initial dose of 15 to 30 mg. is recommended, followed by 15 mg. every 20 to 30 minutes after the first 30 minutes, administered by diluting 6 cc. of the 2.5% solution to 10 cc. with spinal fluid to make a 1.5% concentration (15 mg. per cubic centimeter).

For surface anesthesia, a maximum concentration of 5% may be applied topically by means of cotton applicators, packs, spray, or gargle, depending on the site to be reached. A minimum concentration of 1% may be sufficient for certain minor procedures. For endotracheal intubation, 2 to 10 cc. of a 5% solution may be sprayed on the pharynx and larynx. Gargling with about 5 cc. of the 5% solution may be used prior to bronchoscopy and followed by placement of saturated cotton applicators in the pyriform spaces. For surface anesthesia of the urethral mucous membrane, 5 to 10 cc. of the 5% solution is used by instillation and retention for 5 to 10 minutes in the male urethra; a cotton applicator saturated with the 5% solution is inserted into the female urethra for 10 minutes.

Tests and Standards.—

Physical Properties: Hexylcaine hydrochloride is a white, bitter powder with a slight aromatic odor, m.p. 182-184°. It is freely soluble in alcohol and in chloroform and practically insoluble in ether. The approximate amount that dissolves at 25° in water to form 100 ml. of solution is 6 gm. The pH of a 5% solution is 4.1-4.7.

Identity Tests: Dissolve about 0.1 gm. of hexylcaine hydrochloride in 10 ml. of water and divide the solution into two portions. To one portion add 2 drops of nitric acid and 1 ml. of silver nitrate T.S.: a white precipitate forms, which is insoluble in diluted nitric acid but dissolves in excess ammonia T.S. *(presence of chloride).* To the second portion add 10 ml. of saturated picric acid and 2 drops of diluted sulfuric acid. Place the mixture in a refrigerator for 30 minutes. Scratch the sides of the beaker to effect crystallization. Filter the mixture, wash the precipitate with three 2 ml. portions of cold ether, and dry it at 105° for 15 minutes; the crystals melt at 129-133°. *(Caution! May be explosive. Use safety glass shield.)*

Dissolve 1 gm. of hexylcaine hydrochloride in 15 ml. of water, add 1 ml. of 1 *N* hydrochloric acid and enough water to bring the volume to 25 ml., and run a *U.S.P. heavy metals test:* the amount of heavy metals does not exceed 30 ppm.

A 0.001% solution, prepared as directed in the spectrophotometric assay for hexylcaine hydrochloride, exhibits an ultraviolet absorption maximum at about 232 mμ (specific absorbancy, E[1%, 1 cm.] about 422).

Purity Tests: Dissolve 1 gm. of hexylcaine hydrochloride in 25 ml. of water. Titrate the solution with 0.02 *N* sodium hydroxide, using methyl red T.S. as an indicator: no more than 0.5 ml. of base is required *(absence of appreciable amounts of free acids).*

Dry about 1 gm. of hexylcaine hydrochloride, accurately weighed, in a vacuum desiccator over phosphorus pentoxide for 4 hours: the loss in weight does not exceed 0.1%.

Ignite about 1 gm. of hexylcaine hydrochloride, accurately weighed, cool, and weigh: the residue does not exceed 0.05%.

Assay: (Hexylcaine Hydrochloride) Prepare a 0.001% solution of hexylcaine hydrochloride as follows. Transfer to a 100 ml. volumetric flask 0.1 gm. of hexylcaine hydrochloride, accurately weighed, fill to the mark with 0.1 *N* hydrochloric acid, and mix. Transfer to a second 100 ml. volumetric flask 10 ml. of this solution, fill to the mark with 0.1 *N* hydrochloric acid, and mix. Transfer to a third 100 ml. volumetric flask 10 ml. of this last solution, fill to the mark with 0.1 *N* hydrochloric acid, and mix. Spectrophotometrically determine the absorbancy in a 1 cm. quartz cell at 232 mμ, using 0.1 *N* hydrochloric acid as a blank. The concentration of hexylcaine hydrochloride in the solution in mg./ml. = absorbancy ÷ 42.2. The amount of hexylcaine hydrochloride is not less than 95 nor more than 105%.

(Chloride) Transfer to a 100 ml. volumetric flask about 0.5 gm. of hexylcaine hydrochloride, accurately weighed. Add 25 ml. of water and 3 ml. of nitric acid and mix. Add 50 ml. of 0.1 *N* silver nitrate, accurately measured, and fill to the mark with water. Shake the mixture vigorously and filter it through a dry filter paper. Transfer to a 125 ml. Erlenmeyer flask 50 ml. of the filtrate, accurately measured, and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate, using ferric ammonium sulfate T.S. as an indicator. Each milliliter of 0.1 *N* silver nitrate consumed is equivalent to 0.003546 gm. of chloride and 0.02978 gm. of hexylcaine hydrochloride. The amount of chloride is not less than 11.7 nor more than 12.1%, equivalent to not less than 98 nor more than 102% of hexylcaine hydrochloride.

Dosage Forms of Hexylcaine Hydrochloride

SOLUTIONS. *Physical Properties:* The pH of the solution is 3.1-4.6.

Identity Tests: The solution responds to the picrate and spectrophotometric identity tests for the active ingredient in the monograph for hexylcaine hydrochloride.

Assay: (Hexylcaine Hydrochloride) If the solution contains preservatives, run a preliminary extraction as follows. Transfer to a 125 ml. separatory funnel an amount of solution, accurately measured, equivalent to about 0.1 gm. of hexylcaine hydrochloride. Add enough 0.1 *N* hydrochloric acid to make a total volume of 20 ml., extract with three 20 ml. portions of ether, and combine the extracts in a second 125 ml. separatory funnel. Wash the extracts with three 5 ml. portions of 0.1 *N* hydrochloric acid. Discard the ether extracts and reextract the combined wash solutions with one 10 ml. portion of ether, adding the aqueous phase to the extracted aqueous solution. Transfer the combined aqueous phase to a 100 ml. volumetric flask. If the solution contains no preservatives, merely transfer to a 100 ml. volumetric flask an amount of solution, accurately measured, equivalent to about 0.1 gm. of hexylcaine hydrochloride. In either case, fill to the mark with 0.1 *N* hydrochloric acid and mix. Transfer to a second 100 ml. volumetric flask 10 ml. of this solution, fill to the mark with 0.1 *N* hydrochloric acid, and mix. Transfer to a third 100 ml. volumetric flask 10 ml. of this last solution, fill to the mark with 0.1 *N* hydrochloric acid, and mix. Spectrophotometrically determine the absorbancy in a 1 cm. quartz cell at 232 mμ, using 0.1 *N* hydrochloric acid as a blank. The concentration of hexylcaine hydrochloride in the solution in mg./ml. = absorbancy ÷ 42.2. The amount of hexylcaine hydrochloride is not less than 93 nor more than 107% of the labeled amount.

(Dextrose) Determine the dextrose as directed in the U.S.P. under Dextrose Injection. The amount of dextrose is not less than 95 nor more than 105% of the labeled amount.

Sharp & Dohme, Division of Merck & Co., Inc., Philadelphia.

Solution Cyclaine Hydrochloride 1%: 30 cc. vials. A solution containing 10 mg. of hexylcaine hydrochloride in each cubic centimeter. Preserved with 0.15% methylparaben and 0.02% propylparaben. For infiltration, nerve block, and caudal anesthesia.

Solution Cyclaine Hydrochloride 2.5% with Dextrose 10%: 2 cc. ampuls. A solution containing 25 mg. of hexylcaine hydrochloride and 0.1 gm. of dextrose in each cubic centimeter. For spinal anesthesia.

Solution Cyclaine Hydrochloride 5%: 60 cc. bottles. A solution containing 50 mg. of hexylcaine hydrochloride in each cubic centimeter. Preserved with 0.15% methylparaben and 0.02% propylparaben. For topical anesthesia. U. S. patent 2,486,374. U. S. trademark 426,983.

Neostigmine Methylsulfate-U.S.P. (See New and Nonofficial Remedies 1954, p. 201).

Meyer Chemical Company, Detroit.

Solution Neostigmine Methylsulfate 1:2,000: 1 cc. ampuls. A solution containing 0.5 mg. of neostigmine methylsulfate in each cubic centimeter. Preserved with 0.18% methylparaben and 0.02% propylparaben.

Nicotinamide-U.S.P. (See New and Nonofficial Remedies 1954, p. 555).

The Evron Company, Inc., Chicago.

Tablets Nicotinamide: 25, 50, and 100 mg.

Keith-Victor Pharmacal Company, St. Louis.

Tablets Niacinamide: 25, 50, and 100 mg.

Nicotinic Acid-U.S.P. (See New and Nonofficial Remedies 1954, p. 556).

The Evron Company, Inc., Chicago.

Tablets Niacin: 25, 50, and 100 mg.

Keith-Victor Pharmacal Company, St. Louis.

Tablets Niacin: 25, 50, and 100 mg.

Potassium Penicillin G-U.S.P. (See New and Nonofficial Remedies 1954, p. 148).

Success Chemical Company, Inc., Brooklyn, N. Y.

Tablets Potassium Penicillin G (Buffered): 50,000, 100,000, 200,000, and 250,000 units. Buffered with calcium carbonate.

Pertussis Vaccine, Alum Precipitated-U.S.P. (See New and Nonofficial Remedies 1954, p. 467).

Eli Lilly & Company, Indianapolis.

Pertussis Vaccine (Alum Precipitated): 1.5 cc. (one immunization) and 7.5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with 0.01% thimerosal.

Protein Hydrolysates (See New and Nonofficial Remedies 1954, p. 477).

Mead Johnson & Company, Evansville, Ind.

Solution Amigen 5% with Levugen 10%: 1,000 cc. bottles. Each 100 cc. contains 5 gm. of protein hydrolysate and 10 gm. of fructose. U. S. patent 2,180,637. U. S. trademarks 381,523, 387,310, and 422,992.

Pyrilamine Maleate (See New and Nonofficial Remedies 1954, p. 14).

Keith-Victor Pharmacal Company, St. Louis.

Tablets Pyrilamine Maleate: 25 and 50 mg.

Riboflavin-U.S.P. (See New and Nonofficial Remedies 1954, p. 561).

Keith-Victor Pharmacal Company, St. Louis.

Tablets Riboflavin: 5 and 10 mg.

Secobarbital Sodium (See New and Nonofficial Remedies 1954, p. 301).

The Evron Company, Inc., Chicago.

Capsules Evronal Sodium: 0.1 gm.

Keith-Victor Pharmacal Company, St. Louis.

Capsules Secobarbital Sodium: 0.1 gm.

The Vitarine Company, Inc., New York.

Capsules Secobarbital Sodium: 0.1 gm.

Sulfadiazine-U.S.P. (See New and Nonofficial Remedies 1954, p. 99).

Keith-Victor Pharmacal Company, St. Louis.

Tablets Sulfadiazine: 0.5 gm.

Thiamine Hydrochloride-U.S.P. (See New and Nonofficial Remedies 1954, p. 563).

Keith-Victor Pharmacal Company, St. Louis.

Tablets Thiamine Hydrochloride: 5 and 10 mg.

THE JOURNAL
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EXPENSIVE APPARATUS

One of the forces tending to increase the cost of medical care today is the existence of an endless variety of apparatus that has, or might possibly have, some use in rare cases. The introduction of such apparatus, involving initial laboratory research followed by engineering development, may itself be extremely expensive. But after it has been acquired by an institution there may still be surprising problems of operation, repair, and storage. There are forms of scientific research apparatus, in fact, that remind one of nothing so much as the queen of a termite colony in her subterranean chamber. Especially housed in an air-conditioned room, such apparatus often enjoys the ministration of especially trained persons who do practically nothing else. An infrared spectrometer with rock-salt prisms is a good nonmedical example, but some recent medical apparatus shows similar tendencies.

This creates difficult problems even if there is no doubt whatever about the usefulness of the given apparatus. Examples are respirators and oxygen tents. When they are needed, they are needed badly, and human lives depend on their being available immediately and in perfect working order. When not needed, however, they may tax the storage facilities in a crowded institution. In addition, they may become covered with dust, their metal parts may corrode, chemicals left in them can cake into inert masses, joints may stiffen, plastic parts may crack, an essential nut or bolt may be lost, and, unless these possibilities are watched for, distressing discoveries may be made when the apparatus is taken out in response to an emergency call.

If the apparatus is at all complicated, moreover, someone must learn how to run it. Manufacturers have been known to award certificates in recognition of this achievement. In these days of high personnel turnover, this is not a trivial matter. In a hospital, the frequent rotation of interns, the ceaseless shifting of student nurses, and the restlessness of youthful laboratory technicians aggravate the problem. Instructional books, though anchored to the machine, may prove baffling during the excitement attending an emergency. For this reason, a reliable custodian of apparatus is to be respected, and an older employee who remains at his post through the years can make himself valuable to the institution by alert, conscientious service in this respect.

Perhaps the most difficult problems, however, arise when there is doubt about the usefulness of the given apparatus. The word "given" here takes a double meaning, for sometimes the device has been a gift from a local service club influenced by the blandishment of an enthusiastic promoter. More than one institution has been embarrassed by receiving unwanted apparatus from ill-advised donors and by being expected, moreover, to use it. "I used it," wrote one embattled school nurse in what must have been an understatement, "but discontinued it." Its operation had proved to be so time-consuming that it interfered with her other duties; it had caused trouble with over-referrals to busy doctors, and she got better results with quicker and less expensive methods. She wrote for advice to an independent agency that had evaluated the apparatus, and to her great relief obtained confirmation of her suspicion that the device was unreliable. There is much to be read between the lines of her subsequent letter: "I wish to thank you for your prompt answer to my inquiry. . . . The information did indeed prove helpful, for the disturbance was settled on the basis of your reply. My Supervising Principal and I are most grateful to you."

To the original cost of elaborate diagnostic equipment so much may be added in the way of necessary housing, shielding, plumbing, filtering, and special power supplies that serious consideration must be given to the cost as compared with the value of the anticipated information. An example is furnished by the recent complaint of a staff member in a large and especially progressive hospital. Partly because the staff was genuinely eager to lead in every scientific advance, partly because there is constant pressure from patients who study therapeutics in lay magazines, and partly because this physician had had especially rigorous scientific training and was adept at electronics, he was obliged to construct a formidable apparatus for one group of specialists. Let the instrument be referred to, for convenience, as a metagrabolograph. Clinical reports in praise of metagrabolography, some of them by authors who clearly did not understand their own mathematics, were appearing in the journals. An atlas of metagrabolograms had been printed. Its bibliography listed 700 references to recent European literature. Hopeful manufacturers were unveiling their first models in this country, and specimens were being exhibited at conventions. The challenge could not be ignored. "I gave the idea a thorough trial," said the physician. "Our apparatus had at least forty tubes and a hundred controls. My technicians refused to touch it."

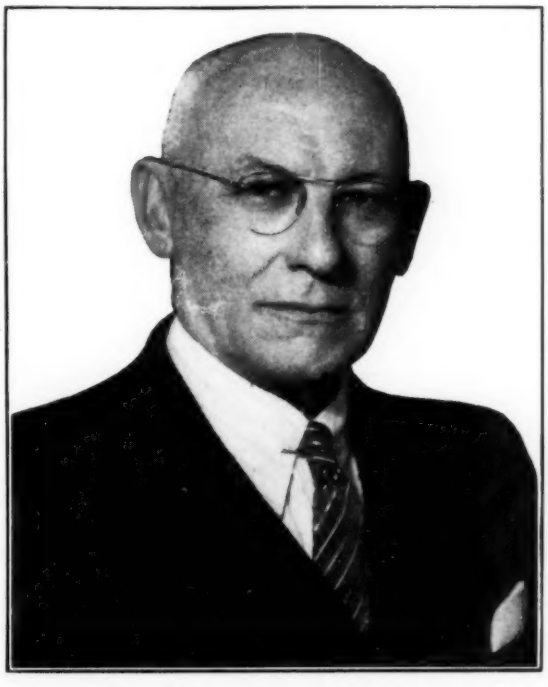
He satisfied himself that neither this apparatus nor anything else based on the same principle could help to determine the prognosis or guide the treatment of the disease in question. He stopped using it, but anticipates trouble, as do some of his colleagues. "I foresee," said one of them, "the usual percentage of uncritical papers appearing in the literature, declaring that the idea has merit, and proving nothing." There may even be a period during which a physician will be suspected of incompetence or accused of carelessness if he cannot swear that he ordered a metagrabologram. If a well-known commentator can complain to the nation because the alleged benefits of a so-called cancer remedy were withheld from a dying Senator, what might such a person not do if some

physician denied a sick general the help of metagrabolography?

It appears that there is a place in medicine for investigators who have the courage to publish negative results, who patiently correct errors that have appeared in print, who question all things and hold fast to that which is good. There is a need for cautious organizations like the scientific councils of the American Medical Association. Someone has to stand fast through bursts of pseudoscience, especially those directed to the public. Unless the medical profession continues to support conservative and critical scientists, the number of expensive gadgets that a hospital must own will increase without limit, and so may the cost of medical care.

DR. ELMER HESS— THE PRESIDENT-ELECT

On June 24, Dr. Elmer Hess of Erie, Pa., was named President-Elect of the American Medical Association by the House of Delegates at the 103rd Annual Meeting in San Francisco. Dr. Hess was born in Millville, N. J., May 31, 1889, received his M.D. from the University of Pennsylvania in 1911, and in World War I served in the Medical Corps of the U. S. Army. He went to France with the American Expeditionary Force and won the Croix de Guerre, the Verdun medal, the Château-Thierry medal, three Silver Star citations, and the Victory medal with five clasps. In 1919, he returned to civil life and took graduate courses in Europe and Johns Hopkins University, Baltimore. Since 1920 he has specialized in urology and is editor and publisher of the *Urolog*, a quarterly bulletin.



ELMER HESS, M.D.
PRESIDENT-ELECT OF THE AMERICAN MEDICAL ASSOCIATION

He is chief of the urological departments at St. Vincent's Hospital and Hamot Hospital in Erie and consulting urologist for the Erie Infants' Home and Hospital, Erie County Tuberculosis Hospital, Corry Hospital, Meadville City Hospital, Erie Veterans Administration Hospital, and Warren State Hospital. He is a fellow of the American College of Surgeons, International Academy of Medicine, and International College of Surgeons. He is also a member of the Canadian Urological Association, Northeastern Section of the American Urological Association, World Medical Association, Pennsylvania State Board of Medical Education and Licensure, the board of trustees of the Pennsylvania Soldiers and Sailors Home and the governing committee of the Gorgas Memorial Institute in Panama. He is a diplomate of the American Board of Urology, honorary member of the Detroit Urological Society, South Central Section, and Western Branch Society of the American Urology Society, and of the Sociedad Chilena de Urologia, and the Brazilian College of Urologists. He is also a corresponding member of the Sociedad Cubana de Urologia and the Sociedad Argentina de Urologia. He is editor for urological subjects for the "Cyclopedia of Medicine, Surgery, and Specialties." He was vice-president of the Pan American Medical Association in 1952-1953.

The office of president of a medical association is nothing new to Dr. Hess. He served as president of the Erie County Medical Society in 1938; of the Medical Society of the State of Pennsylvania in 1947-1948; of the Pan American Medical Association Section on Urology in 1937; of the American Urological Society in 1951-1952; and of the Dr. Hess Urological Foundation. He has long been active in the affairs of the American Medical Association. Dr. Hess has served as a member of the A. M. A. House of Delegates from Pennsylvania since 1946 and as a member of the A. M. A. Council on Medical Service since 1947 (chairman since 1953). He also belongs to the Erie, Kahkwa, and Rotary clubs.

VENEREAL DISEASE CONTROL IS NOT AUTOMATIC

The rapid demobilization of venereal disease control forces after World War I was found in the middle 1930's to have been a serious mistake because it resulted in an upward trend in morbidity from syphilis and gonorrhea in the general population that might have been prevented if control measures had not been curtailed. The interest in this health problem in wartime is laudable, but to argue that it is less important in peacetime is fallacious. Already, increases in case rates for syphilis and gonorrhea have been reported in 28 states and the District of Columbia. A joint statement on this problem by the American Venereal Disease Association, Association of State and Territorial Health officers, and the American Social Hygiene Association [1] offers proof of the need for more attention being focused on this subject. In venereal disease control, as in the control of other communicable diseases, accurate rates for small geographical areas are of vital importance in pinpointing reservoirs of disease that serve as foci for spread to wider areas.

Although there has been a downward trend in reported cases of primary and secondary syphilis, this may mean either fewer cases or a failure to find the new cases. Every

1. Today's VD Control Problem: Joint Statement to the Appropriations Committee of the Federal Congress, 1954, Am. J. Syph. 38: 161-175 (May) 1954.

year the number of reported cases of early latent syphilis has exceeded that of primary and secondary syphilis. This is an indication that more than half of the cases of syphilis go into the latent stage undiscovered, and, as Dr. Thomas Parran [2] has pointed out, "Syphilis can never be controlled while more than one-half of the cases are not recognized for more than one year after onset." Low venereal disease rates for the population as a whole are misleading because the risk is centered in a limited age group (15 to 24 years). The best index of the trend is based on rates for that specific group, but such rates are not generally available. This same age group appears to be most uncooperative in case-finding surveys. It is estimated, however, that there is at present a reservoir of over 2 million persons in this country who need treatment for syphilis, that about 91,000 civilians acquired syphilis in 1953, and that the annual cost of maintaining the syphilitic blind is $12,500,000. The annual incidence of gonorrhea is believed to be over one million cases, and as with syphilis, case finding is more of a problem than treatment of the discovered case.

Most venereal disease patients have more than one (average 3.7) sexual contact. Case-finding interviews that reveal only a fraction of the contacts are wasteful, and for this reason highly trained interviewers are essential. Although great strides have been made in venereal disease control, complete control is far from being accomplished. The venereal diseases are important not only because they are communicable but because they disable and kill. The large undiagnosed, untreated reservoir of these diseases is a potential threat of morbidity and disability. Valuable as antibiotics are, they confer no immunity to reinfection. Despite case finding, treatment, and other control measures, venereal disease will increase unless we take preventive steps when a local upsurge is detected. Case finding must be vigorous in the many small areas of prevalence.

WILLIAM W. BABCOCK, M.D.
AWARDED DISTINGUISHED SERVICE MEDAL

DR. WILLIAM W. BABCOCK AWARDED DISTINGUISHED SERVICE MEDAL

On June 21 at the 103rd Annual Meeting of the American Medical Association in San Francisco, the House of Delegates chose Dr. William Wayne Babcock of Philadelphia as recipient of one of the highest honors in medicine—its Distinguished Service medal, awarded annually for outstanding contributions to medicine and humanity.

Dr. Babcock received the award for the introduction of spinal anesthesia into the United States, for his pioneer work in surgery of the thyroid gland and in bone grafting, and for the designing of several surgical instruments. Dr. Babcock is also credited with the first use of stainless steel wire in abdominal wounds. In addition, he was instrumental in the growth of Temple University, which began as a night school and which now has a medical school of first rank.

Dr. Babcock was born in East Worcester, N. Y., on June 10, 1872, and received his M.D. at the College of Physicians and Surgeons, Baltimore, in 1893. He followed this with postgraduate work at the University of Pennsylvania and was demonstrator and lecturer in pathology and bacteriology at the Medico-Chirurgical College of Philadelphia until 1903, when he became professor of surgery at Temple University, a post he held until 1943. He received an honorary A.M. from Pennsylvania College in 1904, an LL.D. from Temple University in 1932, and an honorary D.Sc. from Ursinus College in 1934 and from the University of Maryland in 1948. In 1943 he became emeritus professor of surgery and clinical surgery at Temple University and acting surgical consultant at the Philadelphia General Hospital.

During World War I, Dr. Babcock was commissioned captain in the Army Medical Corps and was chief surgeon of the base hospital at Fort MacPherson near Atlanta, Ga. He was advanced to the grade of lieutenant colonel and in 1919 returned to civilian life in Philadelphia. He was recipient of the International College of Surgeons' Master Surgeon award and in 1948 was awarded the first Distinguished Alumnus award by the University of Maryland. He is a fellow of the American College of Surgeons and the American Association for the Advancement of Science; honorary member of the Royal Society of Medicine of England; associate member of the Académie de Chirurgie of France; and member of the American Therapeutic Society, of which he was president 1917-1918; Pathological Society of Philadelphia; American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, of which he was president 1933-1944; International College of Surgeons; American Board of Surgery; Société des Chirurgiens de Paris; National Society of Surgeons of Cuba; and the American Medical Association.

Dr. Babcock has written several books and many papers on surgical subjects. As the 17th recipient of the Distinguished Service award he joins a group whose influence on American medicine will be long remembered.

2. Parran, T., Jr.: Syphilis from Epidemiologist's Point of View, Am. J. Pub. Health 22: 141-156 (Feb.) 1932.

MEDICAL NEWS

CALIFORNIA

Health Department Warns Picnickers.—The Health Department of the City of Los Angeles has made available the instruction sheet "Keep Poison Out of Your Picnic" in an attempt to prevent food poisoning from accidental contamination. Free copies may be obtained from the department at 116 Temple St., Los Angeles 12 (MIchigan 5211, ext. 496).

Dr. Merrill Appointed State Director of Public Health.—Dr. Malcolm H. Merrill, deputy director of the state department of public health since 1944, has been appointed by Gov. Goodwin Knight to fill the post of state director of public health following the resignation of Dr. Wilton L. Halverson. The appointment is for the unexpired portion of Dr. Halverson's four year term, which ends Jan. 1, 1956. Dr. Halverson, director of the department since 1943, resigned Feb. 19 to accept appointment as professor of preventive medicine and public health in the University of California at Los Angeles School of Medicine and associate dean of the university's School of Public Health in charge of its Department of Public Health on the Los Angeles campus of the college.

FLORIDA

Personal.—Dr. Ralph Herz, Key West, delivered a special lecture, entitled "Subfascial Fat Herniation as a Cause of Low Back Pain," with presentation of a case, before the Kings County Division of Surgery in Brooklyn, May 17.

Short Course.—The 22nd annual graduate short course for doctors of medicine will be held at the George Washington Hotel in Jacksonville, July 12 to 16. The members of the faculty are: Dr. George T. Harrell Jr., dean, University of Florida College of Medicine, Gainesville; Dr. H. Barton McSwain, associate professor of surgery, Vanderbilt University School of Medicine, Nashville, Tenn.; Dr. Robert E. Cooke, associate professor of pediatrics and physiology, Yale University School of Medicine, New Haven, Conn.; Dr. Conrad G. Collins, professor and chairman, department of obstetrics and gynecology, Tulane University of Louisiana School of Medicine, New Orleans; and Dr. Hans Lowenbach, professor of psychiatry, Duke University School of Medicine, Durham, N. C. On Tuesday and Thursday after the last lecture of the day there will be a boat ride on the St. Johns River (compliments of the George Washington Hotel) honoring the faculty and the attending physicians and their wives. On Wednesday at 5:30 p. m. at a cocktail hour sponsored by Sharp and Dohme, Division of Merck and Company, there will be a reception in honor of Dr. Harrell.

GEORGIA

University News.—The Medical College of Georgia, Augusta, reports that Harland D. Wycoff, Ph.D., assistant professor of oncology, has been awarded a research grant from the Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, to further his study of "The Shwartzman Phenomenon in Tumors," and Dr. Harry B. O'Rear, professor of pediatrics and dean of the faculty, has received a grant from the Georgia Heart Association for continuance in the study of "Action of Sera from Rheumatic Fever Patients on Human Connective Tissue as Demonstrated by Histochemical Techniques."——Dr. John Munn Heng, a graduate in the class of 1954, was given a $1,000 Mead Johnson General Practice Scholarship award, and Dr. Webster A. Sherrer, a resident in pathology, received a grant from the Damon Runyon Memorial Fund for the study of "The Synthesis of Some Phosphorus Fractions in the Particulate Matter of Normal and Hepatoma-Bearing Rats."

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education and public health. Programs should be received at least three weeks before the date of meeting.

INDIANA

Society News.—Officers of the Indiana Roentgen Society for the coming year are Dr. Chester H. Warfield, Fort Wayne, president; Dr. G. W. Ritterman, vice-president; Dr. John A. Robb, Indianapolis, secretary and treasurer.

Personal.—A resolution adopted by the board of directors of the Vanderburgh County Medical Society, commended Dr. Paul D. Crimm, then of Evansville, to his new colleagues and to the people of Sidney, Ohio, and called attention to the fact that Dr. Crimm had received many high honors during his 25 years in the community. Dr. Crimm, a past president of the society and of the Indiana State Medical Association, who has served Vanderburgh County as head of Boehme Tuberculosis Hospital, has entered the private practice of medicine with his brother, Dr. Harry E. Crimm, in Sidney.

Bacteriologists Bestow Pasteur Award.—The Society of Illinois Bacteriologists has named James A. Reyniers, M.S., research professor of bacteriology, University of Notre Dame, South Bend, recipient of the Pasteur award for 1954, "for giving to science a new and powerful tool, the germ-free animal technique." Professor Reyniers is founder and director of Notre Dame's Lobund Institute. He and his associates are credited with having designed and built equipment and developed techniques that make it possible for animals to be born, live a normal life span, and die without ever coming into contact with germs. They recently proved that germs in the mouth are necessary to produce tooth decay. Other research projects underway include studies of radiation sickness, cancer, liver necrosis, antibiotics and growth, protein metabolism, and the role of bacteria in nutrition.

IOWA

Dr. Bierring Honored.—At its annual meeting in Chicago the American College of Physicians bestowed on Dr. Walter L. Bierring, Des Moines, a past president of the American Medical Association, a mastership, the title usually awarded only to former presidents of the college. Dr. Bierring, a former vice-president and regent of the college, was given the honor "as a recognition of personal character, positions of honor and influence, eminence in practice, contributions to organized medicine and other attainments in science and the art of medicine."

Society News.—An Iowa Academy of Surgery was organized at Des Moines, April 26. Dr. Vernon W. Petersen, Clinton, was elected president; Dr. Robert B. Stickler, Des Moines, vice-president; Dr. William R. Bliss, Ames, secretary-treasurer; and Dr. Robert C. Hickey, Iowa City, executive committeeman.——At its annual meeting the Iowa Radiological Society (formerly the Iowa X-Ray Club) chose the following officers: Dr. Arthur P. Echternacht, Fort Dodge, president; Dr. Siegmund F. Singer, Ottumwa, president-elect; Dr. James T. McMillan, Des Moines, secretary-treasurer (reelected). Dr. Wayne K. Cooper, Cedar Rapids, was named to the executive committee.

KANSAS

Society News.—At its meeting in Kansas City, the Kansas Radiological Society elected the following officers: Dr. Willis L. Beller, Topeka, president; Dr. G. Sherman Ripley, Salina, vice-president; and Dr. Abraham M. Cherner, Hays, secretary-treasurer.

McIlvain Career Investigatorship.—The Board of Directors of Community Studies, Inc., and the department of medicine of the University of Kansas School of Medicine, Kansas City, announce the establishment of the McIlvain Career Investigatorship at the school of medicine and the appointment of Dr. Santiago Grisolia as the McIlvain Career Investigator. A grant of $54,000 has been made to the school by Community Studies, Inc., from a trust established by the late Mrs. Frederic E. McIlvain in 1950, who designated her physician, Dr. Sam E.

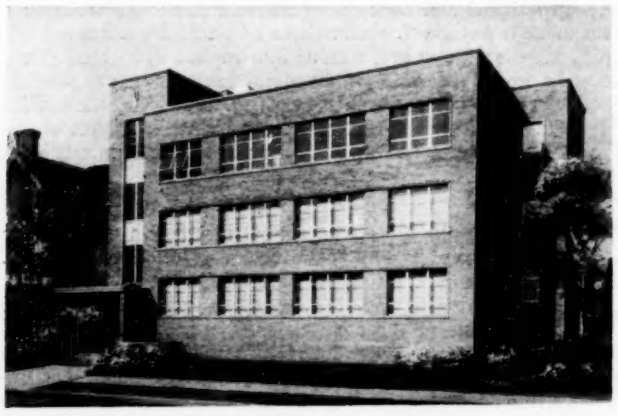
Roberts, Kansas City, Mo., as medical adviser to the trustees. Dr. Grisolia, a graduate of the University of Barcelona Faculty of Medicine, was previously assistant professor of physiological chemistry at the Enzyme Institute, University of Wisconsin, and has received the award of "Established Investigator" from the American Heart Association. At the University of Kansas he will be an associate professor of medicine and biochemistry and a member of the department of medicine and of the Cardiovascular Laboratory.

MAINE

Camp for Handicapped Children.—The Pine Tree Society's Pine Tree Camp at North Pond, Rome, has opened for its 10th season. This camp offers eight weeks of camping to ambulatory handicapped children between the ages of 8 and 16. The staff includes physical, occupational, and speech therapists. The referring physician recommends the desired therapy. Parents are asked to pay what they can afford, but no child is refused if he or she can be helped at camp. Referrals can be sent directly to Pine Tree Society for Crippled Children and Adults, Inc., Bath.

OHIO

Hearing and Speech Center.—The Cleveland Hearing and Speech Center, a Community Chest agency affiliated with Western Reserve University, has opened a new $500,000 addition to its building on the university campus. The addition provides expanded diagnostic, therapeutic, and research facilities



Cleveland Hearing and Speech Center.

for exceptional children. The basement houses the Kresge Hearing and Speech Research Institute, which contains three floated, sound-treated, testing and control units for research in hearing aid evaluation, a radionics laboratory, and auditory training quarters and testing facilities. On the first floor are administrative and therapeutics offices, half the floor space being devoted to the Cleveland Foundation Nursery for Deaf and Multiply Handicapped Children. The second floor has therapy rooms, all with observation and listening facilities for demonstration and orientation of students, parents, and other visiting personnel. It also accommodates a combined auditorium and recreational rehabilitation unit, in which a television screen permits controlled observation of patients being treated in any of the clinical facilities in the building. A multiple recording console enables therapists simultaneously to use the immediate recording and playback equipment from any therapeutic room. The third floor provides a library, faculty room, board room, physiology laboratory, student-staff quarters, and individual research units.

The addition, as seen in the illustration, is part of a million dollar expansion program to enhance the services of the center and to provide training and teaching facilities for close integration of demonstration work and classroom education. Because of closer affiliation with Western Reserve University School of Medicine, the expanded staff will be able to provide improved teaching and demonstration opportunities for medical and nursing students as well as paramedical trainees. The center offers speech and hearing services on a contract basis to the Highland View Cuyahoga County Hospital, three United Cerebral Palsy Association units, Veterans Administration, and two public school districts. Coordinated research activities are projected with the Benjamin Rose and University hospitals. Specialized staff members serve as team participants for cerebral palsy diagnostic clinics at University Hospitals, the Cleveland Clinic, and the Beaumont Cleft Palate Clinic at Mt. Sinai Hospital.

OKLAHOMA

Society Announces Memorial Award.—The Oklahoma Arthritis-Rheumatism Society announces the annual Ian McKenzie award, to be given to the medical student, intern, or resident submitting the best paper on the treatment of arthritis. This award ($50) has been instituted as a memorial to the late Dr. Ian McKenzie of Tulsa. Case presentations (less than 5,000 words) should be submitted in legible form, preferably typewritten, to the secretary of the society, Dr. Richard W. Payne, 625 N. W. 10th St., Oklahoma City, by July 15.

UTAH

Cerebral Palsy Research Program.—The University of Utah College of Medicine, Salt Lake City, is participating in an extensive research program supported by the United Cerebral Palsy Association, designed to provide more knowledge about the functioning of the nervous system. According to Robert W. Doty, Ph.D., assistant professor of physiology, who is directing three investigations in an attempt to explain certain fundamental nervous processes, one of the main purposes of the research is to find whether other portions of the brain can substitute for the missing tissue if injury is sustained very early in life. A second phase of the study concerns the role of movement in learning, to find to what extent the learning of an action is dependent on actually performing it. For this purpose a cataleptic state is induced. In a third series of experiments, electrodes are permanently implanted within the brain substance, and animals are taught to respond to electrical stimulation of various neural structures.

VERMONT

Emergency Medical Call Service.—A new system of answering emergency calls has been adopted by the Chittenden County Medical Society, which has assigned to 66 Burlington physicians the days on which they are to be on "first call" and alternate. The society pays the girls who constitute the "answering bureau" on all emergency calls 24 hours a day, and the girls contact a physician to answer the call.

WEST VIRGINIA

Society News.—A series of paid advertisements sponsored by Kanawha Medical Society in cooperation with Dr. Leon A. Dickerson, head of the Kanawha-Charleston Health Department, have appeared recently in the Charleston papers under the heading, "Your Doctor Speaks." The advertisements, prepared by the public relations committee, headed by Dr. W. Paul Elkin, Charleston, explain the plan, developed by members of the society, to provide medical care for those who believe they cannot afford to go to a physician. Persons living in the Kanawha area who cannot pay for medical service are advised that they should go to the Kanawha-Charleston Health Department or to the office of any one of the 287 members of Kanawha Medical Society to fill out a short-form application for such medical care when needed. The local health department, which maintains a clinic at Memorial Hospital, Charleston, will then investigate, and if the applicant is found to be ineligible for aid from an existing agency or clinic, he will be assigned to one of the members of the society for medical care. The society guarantees the services of a physician in his office in the Charleston area or at a clinic or hospital in Charleston to any patient unable to pay. The emergency call system set up several months ago will be continued without change. In 1951, the service answered 1,850; in 1952, 2,103; and in 1953, 2,380 calls.

GENERAL

Otolaryngologic Examinations.—The American Board of Otolaryngology will conduct the following examinations: Sept. 13 to 17 at the Waldorf-Astoria in New York and March 6 to 10, 1955, at the Hotel Marshall in Richmond, Va.

Book on Occupational Injuries.—The Institute for the Crippled and Disabled, 23rd Street at First Avenue, New York 10, has published a 48-page illustrated book on the rehabilitation of injured workmen with hand and arm injuries. It is a compilation of professional papers presented in April, 1953, at a conference of leading physicians, compensation insurers, officials of government agencies concerned with workmen's compensation matters, and rehabilitation experts of the institute's staff. Copies of the book are available at $1 each, postage prepaid, from the institute; a 25% discount will be given for quantities of 25 or more.

Flights Arranged for Cancer Congress.—The American Cancer Society announces that, in connection with the International Cancer Congress in São Paulo, Brazil, July 23-29, charter flights with Pan American World Airways have been arranged at $521 for the round trip from Miami to São Paulo, with two days in Rio de Janeiro. Insurance companies and commercial aviation underwriters have indicated that all existing and new policies will be in force on these charter flights to the congress. Information concerning the program, travel, or hotel reservations may be procured from the Professional Education Section, American Cancer Society, 47 Beaver St., New York 4.

Hospital Directors of Medical Education.—The initial meeting of an Association of Hospital Directors of Medical Education was held at Atlantic City, N. J., May 3. This new association is composed of physicians whose primary work is the organization and supervision of hospital medical education programs with particular reference to the conduct of internship and residency programs. Most of the members are engaged in the work full time, and the majority are associated with nonuniversity hospitals. The purpose of the association is to foster exchange of ideas and information with the aim of strengthening postgraduate education and training in the hospitals. All physicians with responsibility for hospital programs are invited to membership. Inquiries may be directed to Dr. William J. Lahey, Director of Medical Education, St. Francis Hospital, Hartford, Conn.

Joseph A. Capps Prize.—The Institute of Medicine of Chicago is offering an annual prize of $300 for the most meritorious investigation in medicine or in the specialties of medicine. The investigation may be also in the fundamental sciences, if the work has a definite bearing on some medical problem. Competition for 1954 is open to graduates of Chicago medical schools who completed their internship or one year of laboratory work within a period of five years before Jan. 1, 1954, excluding their terms of service in the armed forces. Manuscripts must be submitted to the Secretary of the Institute of Medicine of Chicago, 86 E. Randolph St., Chicago 1, not later than Dec. 31, 1954.

Life Span Lengthens.—According to the Public Health Service, U. S. Department of Health, Education, and Welfare, the average length of life in the United States has reached a record high of 68½ years, a gain of nearly 4 years in the past decade. The figures, based on death rates prevailing in 1951, are contained in recently published life tables, which show that women on the average outlive men by 6 years, the average lifetime expected for women at birth being 71.8 years and the average for men, 65.9 years. White women at birth have a life expectancy of 72.6 years, compared to 66.6 years for white men. Nonwhite groups have a shorter average life—59.4 years for nonwhite men, and 63.7 years for nonwhite women, but the difference between the two groups has narrowed since 1900, when white persons lived about 15 years longer than nonwhites.

Heart Association Research Awards.—According to a midyear report, the American Heart Association and its affiliates have jointly bestowed 169 awards totaling $953,370.71 on scientists engaged in research in the field of heart and blood vessel diseases, bringing to nearly 8 million dollars the total provided by the association and its affiliates for this purpose in the six years since it became a voluntary health agency. The new awards will support 3 career investigators, 39 established investigators, and 41 research fellows. Also included are 87 grants-in-aid to projects to be conducted by experienced scientists at nonprofit institutions, such as hospitals and medical schools. Studies will be conducted in the fiscal year beginning July 1 in 31 states, the District of Columbia, and 4 foreign countries: Argentina, Canada, Lebanon, and Switzerland.

Special Issue Honors Dr. Novak.—The *Obstetrical and Gynecological Survey* published a special issue (February) in recognition of the 70th birthday of Dr. Emil Novak, assistant professor of gynecology emeritus of the Johns Hopkins University School of Medicine and associate professor of obstetrics at the University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, since 1925. The *Survey*, a bimonthly journal, was inaugurated in 1946 under the joint editorship of Dr. Novak and Dr. Nicholson J. Eastman. Dr. Novak is the author of "Menstruation and Its Disorders," "The Woman Asks the Doctor," "Gynecological and Obstetrical Pathology," "Textbook of Gynecology," and many articles. Dr. Novak was made gynecologist in chief of Bon Secours Hospital in Baltimore in 1939 and holds the same position at St. Agnes Hospital.

Fellowships in Pathology.—The University of Pittsburgh School of Medicine announces the availability of the 1955 Sarah Mellon Scaife fellowships in pathology. This program, designed to prepare men for academic careers principally in the field of pathology, has been established by the department of pathology. The fellowships will provide experience in research, teaching, and diagnostic pathology. Three years will be spent in the department of pathology, University of Pittsburgh, and arrangements will be made for one year at another medical center of the applicant's choice. One fellow will be appointed each year for a four year term and will receive $3,000 in the first year, $3,300 in the second, $3,700 in the third, and $4,000 in the fourth. The candidate, a graduate of an approved medical school, must apply by Nov. 1 for a fellowship beginning July 1 of the following year. Selection will be made by Dec. 15. Information and application forms are available from Dr. Frank J. Dixon, Chairman, Department of Pathology, University of Pittsburgh, Pittsburgh 13.

CARE Sends Drugs to Indo-China.—CARE (Cooperative for American Remittances to Everywhere, Inc.) reports that 1,650,000,000 units of penicillin and 1,000 vials of dehydrostreptomycin, each vial containing one gram of the drug, were recently dispatched to physicians in Indo-China. This action became possible when the Berea College Hospital of Berea, Ky., offered 500 vials of penicillin as a contribution to the CARE program. Several medical drug manufacturers and pharmaceutical houses thereupon contributed penicillin, metal syringes, sodium penicillin, and dehydrostreptomycin. The drugs, flown by Air France from Idlewild, N. Y., to Saigon, Indo-China, have been put at the disposal of the health and sanitation department of the U. S. Operations Mission for the Associated States of Cambodia, Laos, and Vietnam, which will distribute them throughout the three Indo-Chinese countries at particular centers of need. The CARE program aims at providing 300 hospitals, medical schools, and other medical institutions with operation and ward room equipment, instruments, and other supplies. Cash contributions to help CARE defray the shipping cost for these donations may be forwarded to CARE, 660 First Ave., New York 16.

Matas Award.—The Rudolph Matas award in vascular surgery, presented for conspicuous achievements in advancing the progress of surgery of the heart and blood vessels, was recently bestowed on Dr. Emile F. Holman, professor of surgery at Stanford University School of Medicine, Stanford University, San Francisco, and Dr. Michael E. DeBakey, professor and chairman of the department of surgery, Baylor University College of Medicine, Houston, Texas. Both award winners paid tribute to Dr. Matas and reviewed their work in vascular surgery for which they received the award—a gold medallion, bearing a portrait of Dr. Matas in bas-relief, and a watch-key chain.

Dr. Holman was given the award for his experimental and clinical pioneer work on arteriovenous fistulas and the effect of the fistulas on blood circulation in general; for his experimental physiological-pathological work on ductus arteriosus and pulmonary stenosis; and for his original research and current work on aneurysms. Dr. DeBakey received the award for his surgical treatment of aneurysms of the aorta through arterial transplants in which the aneurysms are removed, portions of new blood vessels are transplanted in patients' bodies, and rehabilitation of patients is brought about. His work has been a surgical extension of the primary work in aneurysms by Dr. Matas, who introduced the use of the suture in treatment of aneurysms 66 years ago.

Foreign Medical Education.—Dr. Henry R. O'Brien, U. S. Public Health Service, Washington, D. C., in the March issue of the *Journal of Medical Education* suggests methods to improve medical education abroad without sacrificing the standards of American medical colleges. He believes that a few students from foreign schools should be trained in this country with the idea of eventually returning to their native lands and introducing ideas from U. S. schools. Dr. O'Brien, who suggests the founding of local or regional foreign schools with standards higher than most of those now existing abroad as the best solution to the problem, also recommends an increased exchange of teachers to raise the level of education abroad. The Committee on International Relations in Medical Education of the Association of American Medical Colleges has advocated that medical schools link themselves with a foreign school. In 1951 the Public Health Service and the Economic Cooperation Administration (ECA) made funds available for an exchange of faculty and residents. Washington University began the program by linking with two medical schools in Thailand. ECA, World Health Organization, Fulbright scholarships, the Public Health Service, the Rockefeller Foundation, and others also have given assistance to the program. Dr. O'Brien believes that the increased use of these methods will help to eliminate the problem of foreign students coming to this country to enter our medical schools, only to find they cannot meet the admission standards.

Society News.—At the annual meeting of the **New England Society of Anesthesiologists** in Boston, Dr. Elihu Saklad, Providence, R. I., was elected president; Dr. Richard H. Barrett, Hanover, N. H., vice-president; and Dr. Albert F. Gigot, Boston, secretary-treasurer.——Newly elected officers of the **Gerontological Society** include: Anton J. Carlson, Ph.D., Chicago, president; Miss Ollie A. Randall, New York, president-elect; Nathan W. Shock, Ph.D., Baltimore, secretary; and Dr. J. Esben Kirk, St. Louis, treasurer.——At a recent meeting of the **New England Society of Psychiatry,** the following officers were elected: Dr. Peter B. Hagopian, Hathorne, Mass., president; Dr. Ronald H. Kettle, Norwich, Conn., vice-president; and Dr. Clementine C. McKeon, Bedford, Mass., secretary-treasurer.——At the annual meeting of the **American Academy of General Practice** the following officers were elected: Dr. John R. Fowler, Barre, Mass., president-elect; Dr. John R. Bender, Winston-Salem, N. C., vice-president; Dr. John S. DeTar, Milan, Mich., reelected speaker of the congress of delegates; and Dr. James D. Murphy, Fort Worth, Tex., reelected vice-speaker of the congress of delegates.——At its annual meeting the **American Academy of Allergy** elected the following officers: Dr. John M. Sheldon, Ann Arbor, Mich., president; Dr. Stanley F. Hampton, St. Louis, president-elect; Dr. Joseph Harkavy, New York, vice-president; Dr. Francis C. Lowell, Boston, secretary; Dr. Max Samter, Oak Park, Ill., treasurer; and Dr. Homer A. Howes, Detroit, historian. The next annual meeting will be held in New York Feb. 7 to 9, 1955.——Newly elected officers of the **American Otological Society** include Dr. D. E. Staunton Wishart, Toronto, Canada, president; Dr. William J. McNally, Montreal, Canada, vice-president; Dr. John R. Lindsay, Chicago, secretary-treasurer; and Dr. Henry L. Williams, Rochester, Minn., editor-librarian. The next annual meeting of the society will be held at the Hollywood Beach Hotel, Hollywood, Fla., March 17 and 18, 1955.——The **Myasthenia Gravis Foundation, Inc.,** a nonprofit organization, which recently moved to new headquarters at the New York Academy of Medicine, 2 E. 103rd St., New York 29, announces its first grant, to assist research in the Myasthenia Gravis Clinic at the Massachusetts General Hospital, Boston, under the direction of Dr. Robert S. Schwab. The board of directors of the foundation has voted approval of a grant for myasthenia gravis research at the Johns Hopkins Hospital, Baltimore, and a similar grant for Mt. Sinai Hospital, New York.——At the 75th annual meeting of the **American Laryngological Association,** May 27 and 28, the following officers were elected: president, Dr. Henry B. Orton, Newark, N. J.; vice-presidents, Drs. James H. Maxwell, Ann Arbor, Mich., and Clyde A. Heatly, Rochester, N. Y.; secretary, Dr. Harry P. Schenck, Philadelphia; treasurer, Dr. Fred W. Dixon, Cleveland; librarian, historian, and editor, Dr. Bernard J. McMahon, St. Louis. Dr. Louis H. Clerf, Philadelphia, was presented with the gold medal of the de Roaldes award, and Dr. Henry B. Orton, Newark, N. J., with the Newcomb award. The next annual meeting of the association will be held at the Hollywood Beach Hotel, Hollywood, Fla., March 13 and 14, 1955.——Newly elected officers of the **American Otorhinologic Society for Plastic Surgery** include Dr. Matthew S. Ersner, Philadelphia, president; Dr. Joseph G. Gilbert, Brooklyn, vice-president; Dr. Armand L. Caron, treasurer; and Dr. Louis J. Feit, New York, secretary.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States, its territories, and possessions in the weeks ended as indicated:

Area	June 5, 1954: Paralytic Type	June 5, 1954: Total Cases Reported	June 6, 1953
New England States			
Maine	..	..	..
New Hampshire	..	..	2
Vermont	..	..	..
Massachusetts	..	..	2
Rhode Island	..	..	..
Connecticut	..	2	2
Middle Atlantic States			
New York	1	5	5
New Jersey	..	1	..
Pennsylvania	..	1	1
East North Central States			
Ohio	..	4	4
Indiana	2	3	2
Illinois	1	4	5
Michigan	2	9	5
Wisconsin	2	3	2
West North Central States			
Minnesota	2	2	4
Iowa	..	5	6
Missouri	3	4	3
North Dakota	..	1	1
South Dakota	..	1	2
Nebraska	..	..	4
Kansas	..	1	3
South Atlantic States			
Delaware	..	..	..
Maryland	..	..	4
District of Columbia	..	..	..
Virginia	1	2	3
West Virginia	..	..	2
North Carolina	1	3	13
South Carolina	2	8	4
Georgia	5	13	11
Florida	5	18	8
East South Central States			
Kentucky	..	..	5
Tennessee	..	3	4
Alabama	..	4	17
Mississippi	..	5	9
West South Central States			
Arkansas	1	1	4
Louisiana	7	14	5
Oklahoma	2	6	8
Texas	21	48	56
Mountain States			
Montana	..	..	2
Idaho	..	..	..
Wyoming	..	..	..
Colorado	6	7	1
New Mexico	..	1	..
Arizona	..	6	5
Utah	..	2	1
Nevada	..	1	..
Pacific States			
Washington	..	1	..
Oregon	..	..	3
California	24	37	29
Territories and Possessions			
Alaska	1	1	..
Hawaii	4	7	3
Puerto Rico	..	..	..
Total	93	234	250

LATIN AMERICA

Meeting on Military Medicine.—The first Congresso Brasileiro de Medicina Militar will be held in São Paulo, Brazil, July 11 to 15, under the auspices of the committee of the fourth centennial of São Paulo. The official topics include: health services in combined operations; transportation of the sick and of the wounded by airplanes: indications and contraindications; large-scale production of blood and its substitutes; standardization, production, and storage of drugs to be used in war; organization and functions of health services in naval operations; and therapeutic standards in atomic, bacteriological, and chemical war attacks. Information may be obtained from the congress, at Rua Rodrigo Silva 30-1/o.

International Course on Malaria and Other Metoxenic Diseases.—The School of the Division of Malariology, Department of Public Health, Ministry of Public Health and Social Aid of Venezuela, will give the 11th International Course on Malaria and other Metoxenic Diseases, from July 26 to Dec. 11. The course will be opened to 32 applicants: physicians, officers and engineers in public health, graduates of either national or foreign high schools or universities, and students presently studying public health in the national faculties of universities. To candidates in Latin America, America, and Puerto Rico, the government of Venezuela offers $100 each, payable every two weeks up to Dec. 15. Expenses of the trip to Venezuela are covered by the candidates. The work will include lectures and laboratory and field work. Information may be obtained from Dr. Arturo Luis Berti, Jefe de la Division de Malariologia, Maracay, Aragua, Venezuela.

FOREIGN

Change of Meeting Dates.—The Congress of Neurologists and Psychiatrists of the French-speaking countries will convene in Liege, Belgium, July 19 to 25, instead of the following week, as previously announced (THE JOURNAL, June 19, 1954, page 761). A symposium on myasthenia gravis will be held on Thursday.

Conference on Tuberculosis.—The conference of the International Union Against Tuberculosis will be held in Madrid, Spain, from Sept. 26 to Oct. 2. The official reports are "The Anatomical and Bacteriological Changes of Tuberculosis Lesions Under the Influence of Antibiotic and Chemotherapeutic Treatment," "Place and Choice of Surgical Interventions in Pulmonary Tuberculosis Treated with Antibiotics and Chemotherapy," and "Changes in the Control of Tuberculosis Brought About as a Result of Modern Therapy." A symposium on bovine tuberculosis has been scheduled for Thursday morning. Entertainment will include a Spanish fiesta, a gala banquet, a bull fight, and sight seeing.

DEATHS IN OTHER COUNTRIES

Dr. Raimundo de Castro y Bachiller, professor of legal medicine, University of Havana, Havana, Cuba, died Jan. 14 at the age of 75 of myocardial failure, cardiosclerosis, and chronic pyelonephritis. Born in New York, March 6, 1878, he was graduated from the Columbia University College of Physicians and Surgeons, New York, June 12, 1901. He was licensed to practice medicine in the state of New York and in Cuba. After interning at the Columbus Hospital, New York, he was appointed instructor of hygiene, legal medicine, and toxicology, University of Havana, in 1902, assistant professor in 1917, and full professor in 1923. He founded a museum of Cuban criminology and a laboratory of legal medicine and toxicology with its library, at the Faculty of Medicine of the University of Havana, recognized today as the Institute of Legal Medicine Raimundo de Castro Bachiller for postgraduate studies in forensic medicine. He was secretary of the Academy of Sciences of Havana from 1934 until his death; member of the Junta Nacional de Salubridad y Asistencia Social from 1933; and member of the Consejo Supremo de Defensa Social since its founding in 1938. He was affiliated with the Finlay Institute of Havana and the Sociedad Economica de Amigos del Pais and served as co-director for some years in the *Annals of the Academy of Sciences of Havana.* He was a member of the American Medical Association, the American Public Health Association, the Society of Medical Jurisprudence, the Society of Forensic Medicine of New York, the American Statistical Association of the United States of America, and served as president of the Columbia Alumni Club of Cuba from 1938 until his death. He is the author of "Tratamiento de las intoxicaciones y envenenamientos," "Manual del medico forense cubano," in collaboration with Dr. A. Barreras, and a textbook, "Lecciones de medicina legal y toxicologia" (five volumes with the collaboration of his associates in the school of medicine), and many scientific papers.

MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. George F. Lull, 535 North Dearborn St., Chicago 10, Secretary.

1954 Clinical Meeting, Miami, Florida, Nov. 29-Dec. 2.

1955 Annual Meeting, Atlantic City, N. J., June 6-10.

1955 Clinical Meeting, Boston, Nov. 29-Dec. 2.

1956 Annual Meeting, Chicago, June 11-15.

ALASKA TERRITORIAL MEDICAL ASSOCIATION, Mt. McKinley Park Hotel, Mt. McKinley Park, Aug. 15-17. Dr. William P. Blanton, P.O. Box 2569, Juneau, Secretary.

NATIONAL MEDICAL ASSOCIATION, Washington, D. C., Aug. 9-13. Dr. John T. Givens, 1108 Church St., Norfolk 10, Va., Executive Secretary.

NEUROSURGICAL SOCIETY OF AMERICA, Grand Hotel, Mackinac Island, Mich., July 21-24. Dr. Lester A. Mount, 700 West 168th St., New York 32, Secretary.

RENO SURGICAL SOCIETY, Reno, Nev., Aug. 19-21. Dr. James R. Herz, 508 Humboldt St., Reno, Nev., Secretary.

WEST VIRGINIA STATE MEDICAL ASSOCIATION, The Greenbrier, White Sulphur Springs, Aug. 19-21. Mr. Charles Lively, P.O. Box 1031, Charleston, Executive Secretary.

FOREIGN AND INTERNATIONAL

BRITISH MEDICAL ASSOCIATION, Glasgow, Scotland, July 1-9, 1954. Dr. A. Macrae, B.M.A. House, Tavistock Square, London, W.C.1, England, Secretary.

COMMONWEALTH HEALTH AND TUBERCULOSIS CONFERENCE, Royal Festival Hall, London, England, June 21-25, 1955. Mr. J. H. Harley Williams, Tavistock House North, Tavistock Square, London, W.C.1, England, Secretary General.

CONFERENCE OF INTERNATIONAL UNION AGAINST TUBERCULOSIS, Madrid, Spain, Sept. 26-Oct. 2, 1954. Secretariat, Escuela de Tisiologia, Ciudad Universitaria, Madrid, Spain.

CONGRESS OF INTERNATIONAL ASSOCIATION FOR THE PREVENTION OF BLINDNESS, New York, N. Y., U. S. A., Sept. 12-17, 1954. Professor Franceschetti, 2 Avenue Mirmot, Geneva, Switzerland, Secretary-General.

CONGRESS OF INTERNATIONAL SOCIETY OF MEDICAL HYDROLOGY, Vichy and Paris, France, Sept. 26, 1954. For information write: Dr. Giulio Ammirandoli, Via Della Torretta 11, Montecatini Terme, Italy.

CONGRESS OF INTERNATIONAL SOCIETY OF UROLOGISTS, Athens, Greece, April 1955. Prof. Z. Kairis, 25 rue Voukourestiou, Athens, Greece, Secretary-General.

EUROPEAN SOCIETY OF CARDIOVASCULAR SURGERY, Edinburgh, Scotland, July 9-10, 1954. For information address: Mr. A. J. Slessor, Department of Surgery, University New Building, Edinburgh 8, Scotland.

INTER-AMERICAN CONGRESS OF RADIOLOGY, Shoreham Hotel, Washington, D. C., U. S. A., April 24-29, 1955. Dr. Eugene P. Pendergrass, 3400 Spruce St., Philadelphia 4, Pa., U. S. A., Secretary General.

INTER-AMERICAN SESSION, AMERICAN COLLEGE OF SURGEONS, Universidad Mayor de San Marcos de Lima, Lima, Peru, S. A., Jan. 11-14, 1955. Dr. Michael L. Mason, 40 East Erie St., Chicago 11, Ill., U. S. A., Secretary.

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY, Ambassador Hotel, Los Angeles, Calif., U. S. A., Oct. 10-14, 1954. For information write: Dr. T. H. Seldon, 102-110 Second Avenue S.W., Rochester, Minn., U. S. A.

INTERNATIONAL CANCER CONGRESS, Sao Paulo, Brazil, July 23-29, 1954. Prof. A. Prudente, 171 rua Benjamin Constante, Sao Paulo, Brazil, President.

INTERNATIONAL CONFERENCE ON THROMBOSIS AND EMBOLISM, Basle, Switzerland, July 20-24, 1954. Dr. W. Merz, Chief Medical Officer, Gynecological Clinic, University of Basle, Basle, Switzerland, Hon. Secretary.

INTERNATIONAL CONGRESS OF CLINICAL PATHOLOGY, Washington, D. C., U. S. A., Sept. 6-10, 1954. Dr. Robert A. Moore, Washington University School of Medicine, St. Louis 10, Mo., U. S. A., Chairman, Committee on Arrangements.

INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST, Barcelona, Spain, Oct. 4-8, 1954. Mr. Murray Kornfeld, 112 East Chestnut St., Chicago 11, Ill., U. S. A., Executive Secretary.

INTERNATIONAL CONGRESS ON GROUP PSYCHOTHERAPY, Toronto, Ont., Canada, Aug. 12-14, 1954. Dr. J. L. Moreno, Room 327, 101 Park Ave., New York 17, N. Y., U. S. A., Director of Organizing Committee.

INTERNATIONAL CONGRESS ON GYNECOLOGY AND OBSTETRICS, Geneva, Switzerland, July 26-31, 1954. Dr. H. de Watteville, Maternité Hôpital Cantonal, Geneva, Switzerland, President.

INTERNATIONAL CONGRESS OF HEMATOLOGY, Paris, Sept. 6-11, 1954. Dr. Jean Bernard, 86 rue d'Assas, Paris 6°, France, Secretary.

INTERNATIONAL CONGRESS OF THE HISTORY OF MEDICINE, Rome and Salerno, Italy, Sept. 13-20, 1954. For information write: Segreteria XIV Congresso Internazionale di Storia della Medicina, Instituto di Storia della Medicine, Citta Universitaria, Rome, Italy.

INTERNATIONAL CONGRESS OF HYDATID DISEASE, Madrid, Spain, Sept. 25-30, 1954. Dr. Jesus Calvo Melendro, Hospital Provincial, Sorea, Spain, Secretary General.

INTERNATIONAL CONGRESS FOR INDIVIDUAL PSYCHOLOGY, Zurich Switzerland, July 26-29, 1954. For information write: Dr. E. Schmid, 14, Kronleinstrasse, Zurich, Switzerland.

INTERNATIONAL CONGRESS OF INDUSTRIAL MEDICINE, Naples, Italy, Sept. 13-19, 1954. Professor Scipione Caccuri, Director, Institute of Industrial Medicine Policlinico, Naples, Italy, Chairman, Organizing Committee.

INTERNATIONAL CONGRESS OF INTERNAL MEDICINE, Stockholm, Sweden, Sept. 15-18, 1954. Professor Anders Kristenson, Karolinska Sjukhuset, Stockholm 60, Sweden, Secretary-General.

INTERNATIONAL CONGRESS ON MENTAL HEALTH, University of Toronto, Toronto, Ontario, Canada, Aug. 14-21, 1954. For information write: Executive Officer, International Congress on Mental Health, 111 St. George St., Toronto, Ontario, Canada.

INTERNATIONAL CONGRESS OF NUTRITION, Amsterdam, Netherlands, Sept. 13-17, 1954. Dr. M. van Eekelen, Centraal Instituut voor Voedingsonderzoek T.N.O., 61 Catharynesingel, Utrecht, Netherlands, General Secretary.

INTERNATIONAL CONGRESS OF OPHTHALMOLOGY, University of Montreal and McGill University, Montreal, Canada, Sept. 9-11, 1954, and Waldorf-Astoria, New York, N. Y., U. S. A., Sept. 12-17, 1954. Dr. William L. Benedict, 100 First Avenue Building, Rochester, Minn., U. S. A., Secretary-General.

INTERNATIONAL CONGRESS OF ORTHOPEDIC SURGERY AND TRAUMATOLOGY, Berne, Switzerland, Aug. 30-Sept. 3, 1954. For information write: Professor M. Dubois, Isle-Hospital, Berne, Switzerland.

INTERNATIONAL CONGRESS FOR PSYCHOTHERAPY, Zurich, Switzerland, July 21-24, 1954. Dr. H. K. Fierz, Theaterstrasse 12, Zurich 1, Switzerland, Secretary General.

INTERNATIONAL GERONTOLOGICAL CONGRESS, London and Oxford, England, July 12-22, 1954. Prof. R. E. Tunbridge, General Infirmary, Department of Medicine, The University, Leeds, England, President.

INTERNATIONAL HOSPITAL CONGRESS, Lucerne, Switzerland, May 30-June 3, 1955. Capt. J. E. Stone, International Hospital Federation, 10 Old Jewry, London, E.C.2, England, Hon. Secretary.

INTERNATIONAL INSTITUTE ON CHILD PSYCHIATRY, Toronto, Canada, Aug. 13-14, 1954. Miss Helen Speyer, International Association for Child Psychiatry, 1790 Broadway, New York 19, N. Y., U. S. A., Executive Officer.

INTERNATIONAL POLIOMYELITIS CONGRESS, University of Rome, Orthopedic Clinic, Rome, Italy, Sept. 6-10, 1954. Mr. Stanley E. Henwood, 120 Broadway, New York 5, N. Y., U. S. A., Executive Secretary.

INTERNATIONAL SOCIETY OF BLOOD TRANSFUSION, Paris, France, Sept. 12-19, 1954. For information write: Colonel Julliard, Société Internationale de Transfusion Sanguine, 53 Boulevard Diderot, Paris 12°, France.

INTERNATIONAL SOCIETY FOR CELL BIOLOGY, Leiden, Netherlands, Sept. 1-7, 1954. Professor Peter J. Gaillard, University of Leiden, Leiden, Netherlands, Secretary.

INTERNATIONAL SOCIETY OF GEOGRAPHICAL PATHOLOGY, Washington, D. C., U. S. A., Sept. 6-10, 1954. Professor Fred C. Roulet, Hebelstrasse 24, Basel, Switzerland, Secretary-General.

IRISH MEDICAL ASSOCIATION, Killarney, Ireland, July 7-10, 1954. Dr. P. J. Delaney, 10, Fitzwilliam Place, Dublin, Ireland, Medical Secretary.

JAPAN MEDICAL CONGRESS, Kyoto University and Kyoto Prefectural Medical College, Kyoto, Japan, April 1-5, 1955. Dr. Mitsuharu Goto, University Hospital, Medical Faculty of Kyoto University, Kyoto, Japan, Secretary General.

LATIN AMERICAN CONGRESS ON GYNECOLOGY AND OBSTETRICS, Sao Paulo, Brazil, July 10-15, 1954. Prof. Dr. Jairo Ramos, av. Brigaderio Luiz Antonio, 278-8° andar, Sao Paulo, Brazil, Chairman of Organizing Committee of Medical Congresses.

LATIN AMERICAN CONGRESS ON MENTAL HEALTH, Sao Paulo, Brazil, July 17-22. For information address: Professor A. C. Pacheco e Silva, Avenida Brigadeiro Luiz Antonio 651, Sao Paulo, Brazil.

MEDICAL WOMEN'S INTERNATIONAL ASSOCIATION CONGRESS, Lake Garda, Italy, Sept. 15-21, 1954. Dr. Ada Chree Reid, 118 Riverside Drive, New York 24, N. Y., U. S. A., President.

PAN AMERICAN CONGRESS OF GASTROENTEROLOGY, Sao Paulo, Brazil, July 19-24, 1954. For information address: Dr. Jairo Ramos, Avenida Brigadeiro Luiz Antonio 278-8° andar, Sao Paulo, Brazil.

PAN AMERICAN CONGRESS OF PEDIATRICS, Sao Paulo, Brazil, Aug. 1-7, 1954. For information address: Dr. Jairo Ramos, Avenida Brigaderio Luiz Antonio 278-8° andar, Sao Paulo, Brazil.

PAN AMERICAN HOMEOPATHIC MEDICAL CONGRESS, Hotel Gloria, Rio de Janeiro, Brazil, S. A., Oct. 2-13, 1954. Dr. Paul S. Schantz, 103 West Main St., Ephrata, Pa., U. S. A., Executive Secretary.

PAN-PACIFIC SURGICAL CONGRESS, Honolulu, Hawaii, Oct. 7-18, 1954. Dr. F. J. Pinkerton, Suite 7, Young Bldg., Honolulu 13, Hawaii, Director General.

SOUTH AMERICAN CONGRESS OF ANGIOLOGY, Sao Paulo, Brazil, July 1954. For information write: Dr. Rubens Carlos Mayall, Rua Senador Vergueiro 73, Rio de Janeiro, Brazil, S. A.

WORLD CONGRESS OF CARDIOLOGY, Washington, D. C., U. S. A., Sept. 12-18, 1954. Dr. L. W. Gorham, 44 East 23d St., New York 10, N. Y., U. S. A., Secretary-General.

WORLD CONGRESS OF INTERNATIONAL SOCIETY FOR THE WELFARE OF CRIPPLES, Scheveningen-The Hague, Netherlands, Sept. 13-17, 1954. Secretariat: Miss H. P. Post, Pieter Lastmarkade 37, Amsterdam Z, Netherlands.

WORLD FEDERATION OF OCCUPATIONAL THERAPISTS, Edinburgh, Scotland, August 17, 1954.

WORLD MEDICAL ASSOCIATION, Rome, Italy, Sept. 26-Oct. 2, 1954. Dr. Louis H. Bauer, 345 East 46th St., New York 17, N. Y., U. S. A., Secretary-General.

EXAMINATIONS AND LICENSURE

EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY: *Written.* Various Centers, July 16. Final date for filing applications was Jan 16. Sec., Dr. Curtiss B. Hickox, 80 Seymour St., Hartford 15.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOGY: *Written.* Various centers, Sept. 2. *Oral.* Ann Arbor, Oct. 15-18. To be eligible candidates must have completed thirty-six months of training by October 1. Final date for filing application was May 1. Exec. Sec., Miss Janet Newkirk, 129 E. 52nd St., New York 22.

AMERICAN BOARD OF INTERNAL MEDICINE: *Oral.* New York, Sept. 22-24 (candidates on the east coast). The closing date for acceptance of applications was April 1. *Written* Oct. 18. Final date for acceptance of applications was May 1. *Subspecialties. Allergy.* New York, Sept. 23 and *Pulmonary Disease.* New York, Sept. 24. Closing date for acceptance of applications was May 10. Exec. Sec.-Treas., Dr. William A. Werrell, One West Main St., Madison 3, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: *Oral.* New Haven, November. Final date for filing application is November 1. Sec., Dr. Leonard T. Furlow, 600 S. Kingshighway, St. Louis 10.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: Deadline for receipt of applications is October 1. Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

AMERICAN BOARD OF OPHTHALMOLOGY: *Practical examinations, 1954.* New York City, Dec. 5-9. Final date for filing applications was July 1, 1953. *Written, 1955.* Various cities, Jan. 24-25. Final date for filing application was July 1, 1954. *Practical examinations, 1955.* Chicago, Oct. 9-14. Sec., Dr. Edwin B. Dunphy, 56 Ivie Road, Cape Cottage, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: Final date for filing applications for Part II is Aug. 15. Sec., Dr. Harold A. Sofield, 122 South Michigan Ave., Chicago 3, Ill.

AMERICAN BOARD OF PEDIATRICS: *Oral.* Chicago, Oct. 8-10 and New Haven, December. Ex. Sec., Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PHYSICAL MEDICINE AND REHABILITATION. *Oral and Written.* Washington, D. C., Sept. 5-6. Final date for filing applications was March 31. Sec., Dr. Earl C. Elkins, 30 N. Michigan Ave., Chicago.

AMERICAN BOARD OF PREVENTIVE MEDICINE: *Parts 1 and 2.* Buffalo, Oct. 9-11. Final date for filing applications is July 15. Sec., Dr. Ernest L. Stebbins, 615 N. Wolfe St., Baltimore.

AMERICAN BOARD OF PROCTOLOGY. *Parts I and II.* Philadelphia, Sept. 25-26. *Examination in Proctology and Anorectal Surgery.* Sec., Dr. Louis A. Buie, 102-110 Second Ave., Rochester, Minn. After July 1, 1954 address Dr. Stuart T. Ross, Secretary, 131 Fulton Ave., Hempstead, New York.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: New York, Dec. 13-14; New Orleans, Feb. 28-March 1, 1955; San Francisco, Mid-October, 1955; New York City, December, 1955. Sec., Dr. David A. Boyd, 102-110 Second Ave. S.W., Rochester, Minnesota.

AMERICAN BOARD OF RADIOLOGY: *Oral.* Washington, D. C., September. Final date for filing application for the September examination was May 1. Sec., Dr. B. R. Kirklin, 102-110 Second Ave. S.W., Rochester, Minn.

DEATHS

Kraker, David Aron ⊕ Newark, N. J.; born in New York Jan. 2, 1881; Baltimore University School of Medicine, 1902; past president of the Essex County Medical Society and the Essex County Pathological and Anatomic Society; joined the Medical Corps Reserve of the U. S. Army in 1909; captain, Medical Corps, New Jersey National Guard from 1914 to 1916, when he commanded the New Jersey Field Hospital on the Mexican Border; shortly after the United States entered World War I he was appointed president of the medical examining board, which supervised the procurement of all temporary medical and dental officers for the U. S. Army; organized 50 base hospitals in the United States, and in November, 1917, went to France, where he later became commanding officer of the Toul Hospital group; in 1922 when the 303rd Medical Regiment (U. S. Army Reserve) was organized, he became its commanding officer and served as such for many years; did special work for the government with the rank of brigadier general during World War II; affiliated with the Clara Maass Memorial Hospital, Presbyterian Hospital, Newark Beth Israel Hospital, and the City Hospital, where he was president of the hospital staff from 1946 to 1950; died April 23, aged 73.

Lambert, Charles Irwin ⊕ New York City; born in Argyle, Wis., Dec. 6, 1877; State University of Iowa College of Medicine, Iowa City, 1903; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association and the Association for Research in Nervous and Mental Diseases; instructor in pathology at his alma mater in 1904; for many years professor of psychiatric education at Teachers College, Columbia University, and associate professor of psychiatry at Columbia University College of Physicians and Surgeons; from 1905 to 1913 an assistant in neuropathology for the New York State Psychiatric Institute, and during the latter part of this period also was pathologist at Manhattan State Hospital; from 1913 to 1922 assistant director of Bloomingdale Hospital in White Plains; since 1925 medical director of the Four Winds Hospital in Katonah, N. Y.; consultant at White Plains (N. Y.) Hospital and Northern Westchester Hospital in Mount Kisco, N. Y.; an advisory psychiatrist in the draft service during World Wars I and II; died in Casablanca, Morocco, April 18, aged 76, of coronary thrombosis.

Bradford, Oscar Franklin ⊕ Columbia, Mo.; born in Pleasant Green, Mo., March 2, 1890; Washington University School of Medicine, St. Louis, 1915; member of the American Academy of Pediatrics; specialist certified by the American Board of Pediatrics; served during World War I; instructor in bacteriology and preventive medicine, University of Missouri, 1917-1918; instructor in pediatrics, University of Kansas School of Medicine from 1920 to 1922; from 1919 to 1936 practiced in Kansas City, Mo., where he was affiliated with St. Luke's Hospital, Kansas City General Hospital, and St. Joseph Hospital; affiliated with the University Hospitals, Ellis Fischel State Cancer Hospital, and the Boone County Hospital, where he was past president of the hospital staff; pediatrician to state board of health and postgraduate lecturer to physicians in Missouri from 1936 to 1939; died in the University Hospital March 29, aged 64, of coronary thrombosis.

Lambie, Thomas Alexander ⊕ Bethlehem, Jordan; Western Pennsylvania Medical College, Pittsburgh, 1907; an Affiliate Fellow of the American Medical Association; member of the American Trudeau Society; began his career as a medical missionary of the United Presbyterian Church in 1908 in the Egyptian Sudan; later moved to Addis Ababa in Abyssinia, where he was instrumental in building a 100 bed hospital, the first modern hospital in that country; exiled by the Italians in 1935 when they invaded the country; later joined a Presbyterian Mission and was sent to the Hashemite Kingdom of the Jordan, where he built a tuberculosis hospital and nurses home; wrote several books on travel and religion; died while on a trip to Jerusalem April 14, aged 68, of coronary thrombosis.

⊕ Indicates Member of the American Medical Association.

Holmes, Roy Herbert ⊕ Muskegon, Mich.; born in Grand Rapids, Mich., Jan. 22, 1896; University of Michigan Homeopathic Medical School, Ann Arbor, 1922; member of the American Academy of Dermatology and Syphilology and the Industrial Medical Association; fellow of the American College of Physicians; served during World War II; past president of the Muskegon County Medical Society; chief consultant in dermatology, Hackley Hospital, and consultant in dermatology and syphilology at the Mercy Hospital; formerly editor of the *Journal of the Michigan State Medical Society;* died in Hackley Hospital May 4, aged 58, of coronary occlusion with myocardial infarction.

Strauss, Jerome Frank ⊕ Chicago; Rush Medical College, Chicago, 1912; specialist certified by the American Board of Otolaryngology; formerly clinical associate in otolaryngology at the University of Illinois College of Medicine; member of the American Academy of Ophthalmology and Otolaryngology and the American Laryngological, Rhinological and Otological Society; past president of the Chicago Laryngological Society; served as a medical officer overseas during World War I; senior attending otolaryngologist, Michael Reese Hospital, where he died May 24, aged 65, of coronary thrombosis.

Herzig, Arthur J. ⊕ New York City; Columbia University College of Physicians and Surgeons, New York, 1902; associate professor of otolaryngology at New York Medical College, Flower and Fifth Avenue Hospitals; member of the American Academy of Ophthalmology and Otolaryngology; specialist certified by the American Board of Otolaryngology; attached to the Veterans Administration Hospital in Lyons, N. J., and the Flower and Fifth Avenue Hospitals, where he died May 6, aged 72, of coronary occlusion, myocardial infarction, and arteriosclerotic heart disease.

Abbott, Henry De Van ⊕ Buffalo; New York University Medical College, New York, 1896; an Associate Fellow of the American Medical Association; at one time practiced in Bayonne, N. J., where he was affiliated with Bayonne Hospital; died in Mercy Hospital Feb. 23, aged 88, of uremia.

Bird, Frank Luther ⊕ Netcong, N. J.; University and Bellevue Hospital Medical College, New York, 1915; served during World War I; during World War II headed the medical division of the Morris County Draft Board; affiliated with Dover (N. J.) General Hospital, Newton (N. J.) Memorial Hospital, and Morristown (N. J.) Memorial Hospital; president of the Citizens' National Bank; served as area physician of the Delaware, Lackawanna and Western Railroad; died in the New York Hospital May 9, aged 62, of heart disease.

Bleick, William David, Maplewood, N. J.; University of Pennsylvania Department of Medicine, Philadelphia, 1899; served on the staff of the Presbyterian Hospital, Newark; died May 9, aged 83, of generalized arteriosclerosis.

Boyer, Livingston Stanley, New York City; Meharry Medical College, Nashville, Tenn., 1932; died in the Harlem Hospital March 16, aged 58, of acute coronary occlusion.

Bressmer, Walter Arthur ⊕ Blue Mound, Ill.; Northwestern University Medical School, Chicago, 1915; affiliated with Decatur and Macon Hospital and St. Mary's Hospital in Decatur; died April 12, aged 68, of carcinoma of the rectum.

Brossard, Pierre Mayerie ⊕ Maplewood, Mo.; Washington University School of Medicine, St. Louis, 1905; died in the Deaconess Hospital, St. Louis, April 14, aged 74, of cancer.

Bunting, Henry ⊕ New Haven, Conn.; Harvard Medical School, Boston, 1936; associate professor of pathology at Yale University School of Medicine; specialist certified by the American Board of Pathology; died in Grace-New Haven Community Hospital April 15, aged 43, of glioblastoma multiforme of right frontal lobe.

Connell, John Henry, New Orleans; University of Illinois College of Medicine, Chicago, 1930; formerly assistant professor of pathology and bacteriology at Louisiana State University School of Medicine; specialist certified by the American Board of Pathology; member of the College of American Pathologists and the American Society of Clinical Pathologists; served on the staff of Charity Hospital of Louisiana; pathologist for the Orleans parish coroner's office; died March 2, aged 50.

Connor, Maurice Edward ⊕ Brooklyn; Bellevue Hospital Medical College, New York, 1897; an Associate Fellow of the American Medical Association; for his work with the Selective Service during World War II received a congressional citation; served on the staff of St. Catherine's Hospital; died May 7, aged 77.

Cooley, George P., New Britain, Conn.; Chicago Homeopathic Medical College, 1890; died recently, aged 86, of carcinomatosis and osteoporosis.

Costenbader, Clinton Franklin ⊕ Chicago; University of Virginia Department of Medicine, Charlottesville, 1910; served during World War I; for many years on the staff of the Veterans Administration Hospital; died in the Albert Merritt Billings Hospital May 16, aged 67, of cerebrovascular accident, probably thrombosis, and arteriosclerotic cardiovascular disease.

Cross, Frank Stephen ⊕ Lansing, Mich.; Ohio State University College of Medicine, Columbus, 1936; specialist certified by the American Board of Pediatrics; member of the American Academy of Pediatrics; formerly city health director and school physician; affiliated with Sparrow and St. Lawrence hospitals; died March 31, aged 54, of bronchial asthma and cor pulmonale.

Crowley, Daniel Finbarr, New York City; National University of Ireland, Dublin, 1922; during World War II served with the 93rd Armored Field Artillery Battalion in Sicily and Italy and won the Silver Star decoration; for many years a medical consultant to the Bureau of Social Hygiene, Department of Health; affiliated with City Hospital; died in Doctors Hospital May 5, aged 57, of cirrhosis of the liver.

Currier, Gilman Sterling ⊕ New York City; Columbia University College of Physicians and Surgeons, New York, 1918; certified by the National Board of Medical Examiners; died May 2, aged 58, of coronary thrombosis.

Dodd, Robert Lapsley, Kosciusko, Miss.; Tulane University of Louisiana School of Medicine, New Orleans, 1922; died May 5, aged 60.

Durham, James Richard Sr. ⊕ Wilmington, Del.; Trinity Medical College, Toronto, Canada, 1895; member of the Medical Society of the State of Pennsylvania; served on the staffs of the Warren (Pa.) General Hospital and the Delaware Hospital, where he died April 24, aged 83, of leukemia.

Frenn, Nathan Joseph ⊕ Bark River, Mich.; Marquette University School of Medicine, Milwaukee, 1932; past president of the Upper Peninsula Medical Society; served in France during World War I; president of the medical staff at St. Francis Hospital, Escanaba, where he died April 18, aged 58, of dissecting aneurysm of the thoracic aorta and atherosclerosis of the aorta.

Frymire, William Arthur ⊕ Monmouth, Ill.; University of Illinois College of Medicine, Chicago, 1913; past president of the Warren County Medical Society; for many years medical missionary in Belgian Congo in Africa; served as health officer; died in Monmouth (Ill.) Hospital April 16, aged 70, of cerebral hemorrhage.

Giroux, Alcibiades Alexander, North Mankato, Minn.; School of Medicine and Surgery of Montreal, Faculty of Medicine of the University of Laval at Montreal, Canada, 1908; specialist certified by the American Board of Pediatrics; affiliated with St. Joseph's Hospital in Mankato, where he died March 11, aged 69, of paralysis agitans.

Handly, Lucius Lamar ⊕ Houston, Texas; Tulane University of Louisiana School of Medicine, New Orleans, 1913; associate professor of clinical gynecology at Baylor University College of Medicine; affiliated with St. Joseph's Hospital, Memorial Hospital, and the Methodist Hospital, where he died April 9, aged 64, of coronary occlusion.

Healy, M. Edward ⊕ Chicago; Northwestern University Medical School, Chicago, 1909; an Associate Fellow of the American Medical Association; served during World War I; died May 9, aged 72, of pulmonary edema, chronic myocarditis, and carcinoma of the prostate with pelvic metastases.

Hipp, Richard Raymond ⊕ Whipple, Ariz.; Loyola University School of Medicine, Chicago, 1933; served during World War II; on duty at Veterans Administration Center, where he was ward physician of the tuberculosis service; died March 15, aged 51, of suffocation as the result of a fire in his home.

Howard, Joseph Francis ⊕ Lawrence, Mass.; Harvard Medical School, Boston, 1899; an Associate Fellow of the American Medical Association; served on the staffs of the Mary E. McGowan Memorial Hospital in Methuen, Mass., and the Clover Hill Hospital; director of the Arlington Trust Company; died April 1, aged 78, of heart disease.

Hubbard, Edward Reed ⊕ Berwyn, Pa.; McGill University Faculty of Medicine, Montreal, Canada, 1931; member of the Massachusetts Medical Society, and New England Obstetrical and Gynecological Society; certified by the National Board of Medical Examiners; fellow of the American College of Surgeons; formerly an officer in the M.C., U. S. Naval Reserve; served on the staff of the Morton Hospital in Taunton, Mass.; affiliated with Presbyterian Hospital in Philadelphia; died in Wolfeboro, N. H., April 23, aged 49, of coronary thrombosis.

Hughes, George M., Front Royal, Va.; University of Pennsylvania Department of Medicine, Philadelphia, 1893; died in the Warren Memorial Hospital March 10, aged 84, of coronary thrombosis.

Hurlbut, Edward Franklin ⊕ Meeker, Okla.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1909; died in Oklahoma City April 13, aged 74.

Irey, Paul Raymond ⊕ Plymouth, Ind.; Loyola University School of Medicine, Chicago, 1929; served during World War I; affiliated with St. Joseph's and Northern Indiana Children's hospitals in South Bend and Parkview Hospital in Plymouth; died April 21, aged 58, of coronary occlusion.

Jacobson, Sidney Dattner, New York City; Medical Department of Tulane University of Louisiana, New Orleans, 1890; served during World War I; affiliated with Midtown Hospital; died in St. George, Staten Island, May 4, aged 85, of a heart attack.

Kennedy, Robert Louis ⊕ Metter, Ga.; University of Tennessee College of Medicine, Memphis, 1924; member of the city board of education and city council; died April 1, aged 54, of a heart attack.

Kern, Peter Everett, Cleveland; Ohio State University College of Medicine, Columbus, 1915; died March 6, aged 65, probably of cerebral hemorrhage.

Kilbourn, Edward D., Wichita, Kan.; Northwestern University Medical School, Chicago, 1904; member of the Wichita draft board during World War I; died in Mayo Clinic, Rochester, Minn., April 17, aged 73, of coronary insufficiency and hypertrophy of the prostate with hemorrhage.

McRae, Benjamin Jefferson, Quitman, Miss.; Mississippi Medical College, Meridian, 1907; died in Rush Memorial Hospital, Meridian, April 27, aged 74.

Miller, John, Warsaw, Ill.; College of Physicians and Surgeons, Keokuk, Iowa, 1895; died April 22, aged 84, of hemorrhage from gastric ulcer.

Mills, Charles Street ⊕ Riverton, N. J.; Hahnemann Medical College and Hospital of Philadelphia, 1900; served during World War I; bank president; affiliated with West Jersey Hospital in Camden, where he died April 7, aged 76, of pneumonia.

Minshall, Arthur Gladstone, Northampton, Mass.; M.R.C.S., England, and L.R.C.P., London, 1892; past president of the Hampshire District Medical Society; on the honorary staff of the Cooley Dickinson Hospital, where he was on the staff since 1906 and where he died April 22, aged 85, of bronchopneumonia, diabetes mellitus, and arteriosclerotic heart disease.

Morrey, Charles Bradfield, Columbus, Ohio; Starling Medical College, Columbus, 1896; member of the Society of American Bacteriologists; professor emeritus and formerly chairman of the department of bacteriology, which he established at Ohio State University School of Medicine, where he was professor until 1935; author of "Fundamentals of Bacteriology"; died April 21, aged 84, of arteriosclerotic hypertension and heart failure.

Mullin, Raymond Joseph ⊕ Newark, N. J.; University of Pennsylvania School of Medicine, Philadelphia, 1909; served during World War I; police surgeon; visiting physician at City Hospital, now known as the Martland Medical Center, and past president of its medical board; medical director and for many years on the staff of St. James Hospital, where he died April 18, aged 65, of a cerebral tumor.

Musgrave, George Harrison ⊕ Leesburg, Va.; University of Virginia Department of Medicine, Charlottesville, 1908; served overseas during World War I; on the staff of the Loudoun County Hospital, where he was past president, and member of the board of directors; died April 20, aged 69, of coronary thrombosis.

Mylod, Thomas Francis, Brooklyn; Columbia University College of Physicians and Surgeons, New York, 1894; at one time medical inspector for the New York Health Department, assigned to contagious disease inspection; affiliated with St. Mary's Hospital; died in the Jewish Hospital April 14, aged 83, of renal failure.

Neff, Elmer Ellsworth ⊕ Altoona, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1897; for many years affiliated with Mercy Hospital, where he was one of the founders; died in Altoona Hospital April 21, aged 92.

Nichols, Arthur A., Fargo, N. D.; Washington University School of Medicine, St. Louis, 1906; died in St. Luke's Hospital March 29, aged 69, of gangrene and perforation of the cecum and vascular thrombosis.

Rackley, Grover DeWitt ⊕ Opelousas, La.; Louisiana State University School of Medicine, New Orleans, 1934; served during World War I; died May 1, aged 60, of coronary occlusion.

Reed, Clinton ⊕ Atlanta, Ga.; Atlanta Medical College, 1915; stationed at Walter Reed Hospital in Washington, D. C., during World War I; died in the Crawford Long Hospital April 26, aged 61, of coronary arteriosclerosis.

Riley, Richard Mitchell ⊕ Nutter Fort, W. Va.; Baltimore Medical College, 1908; died April 10, aged 79, after a heart attack.

Rodwell, Thomas Frank ⊕ Mahnomen, Minn.; Detroit College of Medicine, 1886; served during World War I; retired in 1931 after serving for 28 years in the U. S. Indian Service as physician and superintendent at Walker and White Earth; died April 21, aged 92.

Rowe, Alfred Richard ⊕ Poplar Bluff, Mo.; St. Louis University School of Medicine, 1903; served as vice-president of the Missouri State Medical Association and president of the Butler County Medical Society; member of the board of education for many years, and board president at various times; formerly member of the city board of health; died in Poplar Bluff Hospital April 26, aged 78, of cirrhosis of the liver.

Russell, Blinn Whittemore ⊕ Lewiston, Maine; Medical School of Maine, Portland, 1910; member of the Industrial Medical Association; died in Amesbury (Mass.) Hospital recently, aged 70, of carcinoma of the pancreas.

Seavey, Minnie Adelaide ⊕ San Francisco; Cooper Medical College, San Francisco, 1907; an Associate Fellow of the American Medical Association; died April 19, aged 84, of coronary thrombosis, cerebrovascular accident, and arteriosclerosis.

Shea, Cornelius Joseph ⊕ Jersey City, N. J.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1933; member of the Connecticut State Medical Society; served during World War II; affiliated with Jersey City Medical Center, where he died April 24, aged 47, of coronary thrombosis.

Sheets, Fred C., Oklahoma City, Okla.; American College of Medicine and Surgery, Medical Department of Valparaiso University, Chicago, 1906; died in Wesley Hospital April 21, aged 69, of carcinoma of the prostate.

Shepard, Bert H. ⊕ Lowell, Mich.; University of Michigan Medical School, Ann Arbor, 1917; past vice-president of the Kent County Medical Society; member of the staffs of the Blodgett Memorial and St. Mary's hospitals in Grand Rapids, and Ionia County Memorial Hospital in Ionia, Mich.; died April 8, aged 65, of coronary occlusion.

Shively, Charles Francis ⊕ Quaker City, Ohio; Ohio State University College of Medicine, Columbus, 1916; served during World War I; affiliated with St. Francis Hospital, where he died April 21, aged 60, of coronary embolism.

Skinner, Samuel Melville ⊕ Setauket, N. Y.; Long Island College Hospital, Brooklyn, 1922; served on the staffs of Lutheran Hospital and St. Catherine's Hospital in Brooklyn, where he died May 12, aged 56, of cerebral embolism.

Smit, William Maurice ⊕ St. Louis; Chicago College of Medicine and Surgery, 1914; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; formerly senior instructor at St. Louis University School of Medicine; served on the staffs of the Jewish Hospital, St. Mary's Group of Hospitals, and the Missouri Pacific Hospital, where he died March 14, aged 72.

Smith, George Franklin, Chicago; Washington University School of Medicine, St. Louis, 1910; died in the Henrotin Hospital May 5, aged 71, of coronary thrombosis.

Smithwick, John W. P., La Grange, N. C.; University of Maryland School of Medicine, Baltimore, 1895; died March 24, aged 83, of senility.

Souchon, Marion Sims ⊕ New Orleans; Medical Department of Tulane University of Louisiana, New Orleans, 1894; at one time on the faculty of his alma mater; fellow of the American College of Surgeons; served on the staff of the Charity Hospital; one of the founders, vice-president, and medical director of the Pan American Life Insurance Company; died April 2, aged 83, of aortic stenosis, cardiac hypertrophy, and arteriosclerosis.

Spivey, James Langdon ⊕ Wichita Falls, Texas; Columbia University College of Physicians and Surgeons, New York, 1920; affiliated with Wichita Falls State Hospital, where he died April 19, aged 59, of hepatic coma and cirrhosis.

Sprecher, Samuel, Chicago; Illinois Medical College, Chicago, 1902; served on the staffs of the Swedish Covenant and American hospitals; died in Chickasha, Okla., April 19, aged 87, of cerebral hemorrhage.

Starr, Russell Wood ⊕ Los Angeles; College of Medical Evangelists, Loma Linda and Los Angeles, 1923; member of the Industrial Medical Association and the American Academy of General Practice; served during World War I; on the staff of the California Lutheran Hospital; died April 8, aged 57, of coronary thrombosis and splenic infarct.

Steiner, Milton Byrd ⊕ Portland, Ore.; University of Oregon Medical School, Portland, 1927; specialist certified by the American Board of Otolaryngology; member of the Pacific Coast Oto-Ophthalmological Society; served during World War II; formerly on the faculty of his alma mater; affiliated with St. Vincent's Hospital; died April 24, aged 51, of cancer.

Storm, George Randolph ⊕ Helena, Ark.; Jefferson Medical College of Philadelphia, 1913; served during World War I; died April 2, aged 64, of coronary occlusion.

Stratte, Joseph John ⊕ Grand Forks, N. D.; University of Minnesota Medical School, Minneapolis, 1915; died in Minneapolis April 9, aged 67, of a heart attack.

Strowger, Charles William, Rochester, N. Y.; New York Homeopathic Medical College and Hospital, New York, 1906; served during World War I; died in Clifton Springs (N. Y.) Sanitarium and Clinic April 9, aged 71, of carcinoma of the bladder and stricture of urethra due to infection.

Sullivan, Elizabeth Ann, Cambridge, Mass.; Tufts College Medical School, Boston, 1914; trustee of the Cambridge Home for Aged; died April 8, aged 61, of cancer of the colon.

Swanson, Charles Francis ⊕ Los Angeles; Chicago College of Medicine and Surgery, 1910; died March 17, aged 71.

Sweetland, George James ⊕ Constantine, Mich.; Grand Rapids Medical College, 1900; past president of St. Joseph County Medical Society; past president of the school board; veteran of the Spanish-American War; on the staff of Three Rivers (Mich.) Hospital where he died March 29, aged 81, of uremia and arteriosclerosis.

Sylvester, Philip Haskell ⊕ Damariscotta, Maine; Harvard Medical School, Boston, 1906; specialist certified by the American Board of Pediatrics; member of the American Academy of Pediatrics and the New England Pediatric Society; visiting and consulting physician, Miles Memorial Hospital; chief of pediatrics, Bath (Maine) Memorial Hospital; formerly practiced in Boston, where he was emeritus associate visiting physician at Children's Hospital; died March 12, aged 73, of coronary occlusion.

Thompson, George Matthew, Rochester, N. Y.; Hering Medical College, Chicago, 1898; died in the Strong Memorial Hospital April 22, aged 82, of a fractured skull and cerebral hemorrhage.

Vollborn, Albert Lawrence, Altadena, Calif.; Illinois Medical College, Chicago, 1904; died in Lake View Hospital in Danville, Ill., April 22, aged 81, of fracture of the right femur as the result of a fall.

Waters, William Joseph, Chicago; Bennett Medical College, Chicago, 1914; on the staff of the Provident Hospital, where he died June 7, aged 74.

Weed, Frank Elmer ⊕ Park River, N. D.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1912; member of the North Dakota State Board of Medical Examiners; fellow of the International College of Surgeons: member of the American Trudeau Society; health officer; served during World War I; affiliated with Deaconess and St. Joseph's Community hospitals in Grafton and St. Ansgars Hospital, where he died March 9, aged 65, of carcinoma of the lung.

Weis, William Daniel ⊕ Munster, Ind.; Chicago College of Medicine and Surgery, 1904; resigned in 1952 as health officer of Lake County, a post he held for 18 years; for many years city health officer of Hammond, where he served on the staff of St. Margaret Hospital, and as president of the Citizens National Bank; died April 18, aged 80, of bacterial endocarditis and valvular heart disease.

Wells, Edwin Mercer, Bellingham, Wash.; Kentucky School of Medicine, Louisville, 1892; served during World War I; died May 2, aged 87.

Wersebe, Frederic William ⊕ Washington, Conn.; New York University Medical College, New York, 1898; past president of the Litchfield County Medical Society; chairman of the board of education for many years; health officer of the town of Washington from 1911 to 1953; served on the staffs of the Danbury (Conn.) Hospital and New Milford (Conn.) Hospital; died in New Haven Hospital May 8, aged 76, of chronic pulmonary fibrosis and emphysema.

Wethall, Anton G. ⊕ Minneapolis; University of Minnesota College of Medicine and Surgery, Minneapolis, 1903; member of the American Urological Association; specialist certified by the American Board of Urology; formerly clinical assistant professor of urology at his alma mater, now the University of Minnesota Medical School; served on the staffs of the Deaconess, St. Andrew's, and Mount Sinai hospitals; died April 4, aged 81, of myocardial insufficiency due to coronary sclerosis.

Whaley, Thomas Bravard ⊕ Princess Anne, Md.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1924; served during World War II; affiliated with Peninsula General Hospital in Salisbury; died May 15, aged 52, of injuries received in an automobile accident.

White, James Ryland ⊕ Ben Hill, Ga.; Emory University School of Medicine, Atlanta, 1926; during World War II chief medical examiner for Selective Service Local Board No. 61 of Fulton County; served on the staffs of the Piedmont, Georgia Baptist, and Crawford W. Long Memorial hospitals in Atlanta; died May 11, aged 51, of cerebral hemorrhage.

Whitham, Roy Herbert ⊕ Lincoln, Neb.; Harvard Medical School, Boston, 1924; certified by the National Board of Medical Examiners; specialist certified by the American Board of Surgery; a private in the Students Army Training Corps during World War I; served during World War II; past president of the Lancaster County Medical Society; attending surgeon Bryan Memorial, Lincoln General, and Nebraska Orthopedic hospitals; consulting surgeon, Lincoln State Hospital; died April 7, aged 54, of coronary occlusion.

Wilkerson, George Hiram, Mobile, Ala.; Meharry Medical College, Nashville, Tenn., 1897; died March 26, aged 82, of carcinoma of the stomach.

Williams, Charles Tarleton ⊕ New Orleans; Tulane University of Louisiana School of Medicine, New Orleans, 1924; member of the American Academy of Pediatrics; served during World War I; formerly affiliated with Touro Infirmary, Baptist Hospital, and Mercy Hospital; died in Pearl River, La., March 29, aged 66, of cerebral hemorrhage.

Woelfle, Henry Ewald ⊕ Maplewood, N. J.; Cornell University Medical College, New York, 1902; died in West Palm Beach, Fla., April 1, aged 75, of coronary occlusion.

Wolf, George David ⊕ New York City; University and Bellevue Hospital Medical College, New York, 1913; specialist certified by the American Board of Otolaryngology; served as assistant clinical professor of otolaryngology at New York Medical College, Flower and Fifth Avenue Hospitals; associated with Flower and Fifth Avenue Hospitals; author of "The Physician's Business" and "Ear, Nose and Throat: Symptoms, Diagnosis and Treatment"; died April 13, aged 69, of a heart attack.

Wolff, George Samuel, Brooklyn; Long Island College Hospital, Brooklyn, 1907; died in Jacksonville, Fla., April 1, aged 68, of coronary thrombosis.

Wood, Charles Milton ⊕ Sacramento, Calif.; University of Southern California School of Medicine, Los Angeles, 1936; served during World War II; affiliated with Sacramento County, Sutter, and Mercy hospitals; died April 18, aged 45.

Wood, John William, Mount Gilead, Ohio; Jefferson Medical College of Philadelphia, 1895; died April 28, aged 84, of injuries received when a train struck the truck in which he was riding.

Woodruff, William Anderson ⊕ Woodruff, S. C.; Medical College of the State of South Carolina, Charleston, 1905; past president of the Pickens County Medical Association, Spartanburg County Medical Association, and the Fourth District Medical Association; for two years a member of the state legislature from Spartanburg County; honorary member of the board of trustees at his alma mater, at which he became member of the board in 1920; served as a member of the local school board of trustees; died April 9, aged 77, of coronary thrombosis.

Woolery, Kirtley Benton, Falmouth, Ky.; Kentucky School of Medicine, Louisville, 1904; served during World War I; for many years police judge of Falmouth; died March 29, aged 73, of coronary thrombosis.

Woolwine, Charles Rollin ⊕ Sealston, Va.; Medical College of Virginia, Richmond, 1908; retired health officer, Virginia Polytechnic Institute in Blacksburg, a post held for 23 years; died in Medical College of Virginia Hospital Division, Richmond, March 19, aged 73, of Hodgkin's disease.

Yauman, Claude Foster, Youngstown, Ohio; Eclectic Medical College, Cincinnati, 1915; on the staff of the Youngstown Hospital Association; died April 21, aged 66, of calcarous aortic stenosis.

Young, James Dapsie, Fayette, Ala.; Memphis (Tenn.) Hospital Medical College, 1894; died in McNease and Robertson Hospital April 20, aged 85, of cardiovascular disease.

FOREIGN LETTERS

ENGLAND

Fellowship for Freedom in Medicine Criticizes Health Service.—The executive committee of the Fellowship for Freedom in Medicine, whose chairman is Lord Horder, has submitted a memorandum to the Guillebaud Committee, appointed to inquire into the cost of the National Health Service. It says that the main cause of the high cost of the service lies in the inadequately considered and faulty structure of the service itself. Its fundamental defect is that it is based on the hospital and not the general practitioner; this is considered to be bad medicine and bad economics. The fellowship has a four point plan to remedy the defects of the service. It suggests (1) making the family physician the pivot of the service, by raising his status, which has been undermined, and by encouraging him to practice good medicine; (2) reducing the excessive and unnecessary use of the hospitals; (3) placing increased responsibility on the patient for his use of the health service; and (4) freeing medicine from party politics. The fellowship deprecates making nearly everything free to the citizen. Getting everything for nothing develops not only a child-like dependence on the state, but also a childish irresponsibility toward the welfare of the individual. The public should be educated to make intelligent use of the service and not to get as much as they can for what they have paid in weekly contributions. Many patients are frustrated and dissatisfied because the physician has no time to talk over their problems with them; he has time only for those who appear really ill. Good medicine requires an unhurried approach. Those who can afford to pay, says the fellowship, should do so. It is difficult to believe that the average citizen cannot pay more for what he actually receives in medical care when it is considered that money spent on alcohol, tobacco, movies, and betting would pay for the health service more than twice over.

The fellowship believes that there has been a deterioration in medical standards, particularly in general practice, and that, if the state ever had a monopoly in medicine, these lowered standards would become the rule and the art of general practice would be lost forever. Independent practice, with its competition and stimulus to provide the best, is the answer to this. There is evidence that many general practitioners are discontented and that the physician-patient relationship has been seriously disturbed. The average physician cannot look after 4,000 patients as allowed under National Health Service; his attention with a list this size must be perfunctory and the seriously ill or those in need of accurate diagnosis must be referred to a hospital. Little wonder that the status of the general practitioner has seriously declined in the eyes of the patient, who has the whip hand as he can transfer elsewhere without much trouble.

The way to save money, says the fellowship, is to keep people out of hospitals by increasing the status, scope, and remuneration of the general practitioner. Experience, good work, and higher qualifications should be taken into consideration in assessing a general practitioner's worth. The importance of general practitioner hospitals and general practitioner appointments in hospitals as means of advancing standards is stressed. The return of the right to sell the good will of a practice is also advocated. In the hospital service, there is excessive centralization with lack of freedom and responsibility at the periphery. Hospital staffs are discontented because of lack of any effective professional voice in hospital affairs and in making staff appointments. The high cost of an increasing lay administrative staff is also pointed out. Although the regional hospital boards are necessary for general coordination, their functions could be curtailed with advantage, and those appointed to committees and boards should be selected in the interests of the hospital service and not for their political affiliations. The fellowship suggests an alternative administrative structure for the National Health Service. It advocates a national health board with Parliamentary and ministerial control over it similar to that for nationalized industries.

The items in these letters are contributed by regular correspondents in the various foreign countries.

Continuous Infusion for Relief of Anuria.—Prolonged anuria has been treated by exchange transfusions, peritoneal dialysis, and use of the artificial kidney. Prof. Scott Russell and his colleagues have devised yet another method—continuous infusion through a catheter in the inferior or superior vena cava (*Lancet* **1**:902, 1954). The patient with prolonged anuria should be provided with 1,600 calories daily to reduce endogenous tissue breakdown and with up to 1 liter of water. Normally this can be given by an intragastric drip, but persistent vomiting may preclude this form of administration. In such cases Professor Russell and his colleagues administer 1 liter of 40% dextrose solution daily by a continuous infusion. This cannot be given in a peripheral vein because of the danger of thrombosis. A 4 mm. polythene catheter is inserted into the upper end of the saphenous vein and passed 8 to 10 in. into the inferior vena cava. Dilution is so rapid that there is no danger of thrombosis. If thrombophlebitis threatens, the catheter is removed and another inserted in the median antecubital vein and passed along the basilic vein to the subclavian vein and under fluoroscopy into the superior vena cava. The infusion is then continued. Any fluid or electrolyte loss from vomiting is corrected by adding sodium and potassium chloride, equivalent to that lost, dissolved in a 5% salt solution. Frequent estimations of blood electrolytes are made so that the necessary corrections can be made. Insulin (30 to 60 units daily) is also necessary to balance the large amount of carbohydrate (400 gm. daily). The chief dangers are thrombophlebitis and infection, which are prevented by incorporating 15,000 units of heparin and penicillin in the 24 hour infusion. By using this method, the patient's nutritional requirements can be supplied for three weeks. A patient treated by this method was completely anuric for 11 days and partially so for another 10 days. Recovery was ultimately complete, although there was slight residual impairment of kidney function.

Prevention of Dental Decay.—In May, 1954, the Child Dental Health Committee of the British Dental Association reported on the dental health of children to the Minister of Health, Minister of Education, and other public bodies. A national campaign to prevent dental decay in children instead of using costly and ineffective methods of restoring and replacing diseased teeth is recommended. The committee urges testing the value of fluoridating water supplies as a means of reducing dental caries in children. Mr. Stewart Ross, chairman of the Council of the International Dental Federation, commented at a press conference on May 3 that American experience showed that fluoridation of water reduced the incidence of dental caries in children by about half. It should be possible to make a controlled test in Britain because North Shields had an adequate supply of fluorine in the drinking water, whereas South Shields did not. If fluorine was an important factor in preventing dental decay, the effect should be seen by observing the incidence of dental decay in the two towns. The committee also recommends that the school dental service be transferred from the local authority to the Ministry of Health. School children are at present receiving inadequate dental care because of the difficulty of obtaining school dentists, who are inadequately paid by the local authority. Parents and teachers should be warned of the bad habit of giving children sweets between meals. This, and the giving of sweets, biscuits, and sweetened liquids at bedtime, is considered to be a potent factor in causing dental decay. In Britain only one person in 50 has sound teeth, and it is estimated that only 17 million toothbrushes are bought a year by a population of 50 million.

Litigation Against Hospitals.—In the past when a hospital physician and the hospital authority were involved in negligence suits, the authority, in exonerating itself, sometimes tried to throw the blame on the medical staff. This was often prejudicial to the successful conduct of the defense of hospital and physician. Discussion between the Council of the British Medical Association and the Ministry of Health has recently been held

on the problem of litigation against hospitals and their medical staff. They have now agreed that the hospital authority and the physician involved, or his defense society, should try to reach an agreement beforehand on the way in which damages awarded to the plaintiff shall be apportioned or that, failing to agree, they will bear the damages in equal shares. This agreement is operative from April 1 (*Circular H. M.* **54:**2), and copies of it have been sent to all hospital authorities. Where both hospital authority and one or more hospital physicians are cited as defendants, the British Medical Association and the Ministry of Health have agreed that: 1. A defendant may, on notifying the other party, settle the case out of court, but he must accept sole responsibility for payment of the whole sum for which the case is settled. 2. If the defendants settle out of court, the payment made to the plaintiff shall be borne between the defendants agreed to be liable in such proportion as they may agree between themselves or, in default of agreement on the proportions, in equal shares. 3. If the defendants agree to defend the action in court, the procedure should be (*a*) the defendants should try to agree before the action comes to court on the proportion in which any damages and costs that may be awarded to the plaintiff shall be borne between them; (*b*) if this is not possible, the defendants should try to reach such agreement after the trial of the action; and (*c*) failing agreement under (*a*) or (*b*), the damages and costs awarded to the plaintiff shall be borne in equal shares between the defendants held liable. 4. In exceptional circumstances in which some important legal or professional principle is involved, any defendant may give notice to the other before delivery of defense by either party that paragraphs 1 to 3 shall not apply, and the normal legal processes will then be open to all defendants.

Where either the hospital authority alone or a hospital physician is cited as defendant in an action, the defendant will have complete discretion whether to contest the action or to settle out of court. The hospital or the physician concerned shall not take legal action to obtain a contribution from the other, nor cite the other unless requested to do so. It is recognized, however, that a case may arise in which, although a hospital physician may not be cited, he or his defense society might properly be asked to make a payment toward any damages awarded the plaintiff because his action was a material factor in the negligence complained of. Conversely, under certain circumstances the hospital authority might be asked to make a similar payment.

Salary Rise for Specialists and Hospital Physicians.—During the last six years the earnings of the industrial worker in Britain have increased by 50%. General practitioners as a group, although not individually, have secured a rise of about a third of their income by virtue of the Danckwerts arbitration award of 1952. Hospital physicians and specialists working in hospitals were promised an increase in remuneration six years ago when the National Health Service was introduced. This has only just been awarded and is equivalent roughly to an increase of 10%. A committee, known as the Spens Committee, fixed physicians' salaries under the National Health Service in 1948 on the basis of 1939 money values. In spite of repeated protests, the Ministry of Health declined to adjust remuneration to correspond to the postwar cost of living. A special committee of the Medical Whitley Council, appointed to deal with the problem, has now recommended increases in pay, and these have been agreed on by the Ministry of Health. The basic scale for specialists in hospitals will be increased by £400 per annum at the minimum level and £350 at the maximum level. A specialist on starting his appointment, at about age 32, now receives a basic salary of £2,100 per annum, instead of £1,700 and reaches a maximum of £3,100 instead of £2,750 at age 40. Junior hospital medical officers are to receive increases from £75 to £200 above the 1948 salary scale. In 1948 the Spens Committee considered that top flight specialists should receive £5,000 per annum in terms of 1939 values of money. All present-day salaries fall far short of this. The British Medical Association is dissatisfied with the recommendations. In an editorial in the *British Medical Journal* (April 10, 1954, p. 860) the writer says that it is difficult to see on what basis the increases were determined and that the negotiators were not armed with the facts that an expert economist would have given them.

Tuberculous Meningitis.—The overriding factor in the prognosis of tuberculous meningitis is the stage the disease has reached when treatment is begun. The diagnosis of the disease in the early stages may be difficult. When evidence of active systemic tuberculosis is lacking, the clinical findings are those of mild meningeal inflammation. The cerebrospinal fluid findings in the early stages may not always be clear cut. The differential diagnosis is from virus infection of the central nervous system, spirochetal infections, brain abscess or tumor, and benign lymphocytic meningitis. If the disease is early tuberculous meningitis, to wait until the disease is established before instituting treatment may be to wait until it is too late to save the patient. Taylor, Smith, and Hunter (*Lancet* **1:**700, 1954) claim that in difficult cases the diagnosis of tuberculous meningitis can be facilitated by observing the distribution of bromide ions in the serum and spinal fluid. In the absence of disease of the central nervous system, the serum-spinal fluid bromide ratio is 2 or 3 to 1. The authors found that the introduction of tuberculin into the spinal fluid of Mantoux-positive subjects with normal meninges and without active tuberculosis abolished the blood-spinal fluid barrier to bromide ions. In other words the serum-spinal fluid bromide ratio fell to unity. Active tuberculous meningitis has the same effect on the blood-spinal fluid barrier. They examined the serum-spinal fluid bromide ratio in 33 patients with early tuberculous meningitis, in whom the diagnosis was confirmed by isolation of Mycobacterium tuberculosis from the spinal fluid. In most patients the ratio was between 0.7 and 1.29, and in only 3 was it higher than 1.6. In controls suffering from nontuberculous meningitis the ratio was over 1.6 in 31 out of 33 cases. These findings also support the view put forward by the late Sir Hugh Cairns in 1952 that changes in the spinal fluid in tuberculous meningitis are the expression of a spontaneous intrathecal tuberculin reaction, i. e., antibody-antigen response. The authors are careful to point out that a low bromide serum-spinal fluid ratio is not pathognomonic of tuberculous meningitis. They claim that it is only an aid to diagnosis when considered in conjunction with the other clinical and pathological findings.

ITALY

Society of Chemotherapy.—The Italian Society of Chemotherapy, which was established several months ago by Prof. Emilio Trabucchi, held its first meeting to discuss antimitotics. Professor Trabucchi's report on their pharmacology aimed at a systematic classification of the various poisons of mitosis according to their mechanism of action. Among the substances capable of preventing the synthesis or use of those purine and pyrimidine structures that are necessary for the elaboration of the large nucleic complexes should be included the preparations that are antagonistic to folic acid—they are used in the treatment of some forms of leukemia—and also purines, such as 6-mercapto-purine, that are modified in various ways. Acriflavine hydrochloride (Trypaflavine) and analogous substances may be considered to be mitostatic because they give rise to a real and true "mitotic silence."

Some antimitotic drugs exert their action at a later phase of mitosis—at the moment in which the nuclear membrane divides and before the spindle is formed—by blocking the mitosis and arresting it at the prophase. Among the drugs of this group are choline and other quaternary bases of ammonium, and, because these two are valuable in many fields of pharmacology and therapy, much work is being done with them. Other substances prevent mitosis during the formation of the spindle by interfering with the gelation that precedes the formation of the spindle. These include some of the anticoagulants, such as heparin, treburon, and sulfurated substances. These substances have a true antimitotic action, but, although their activity has already been tested experimentally on various types of tumors, it is still premature to use them in the treatment of neoplasms. Some substances that have a true antimitotic action similar to that of heparin and heparin-like preparations have been introduced in industries because they can remove calcium from compounds such as calcium oxalate. One of these is ethylenediaminetetracetic acid and its sodium salt (Versene or Sequestrene) that

has been used for several years as a water softener and for removing crusts from boilers. Today it is being tried in the treatment of some forms of urinary lithiasis.

Colchicine, its derivatives, and other substances, such as quinacrine (Atabrine) hydrochloride, with a similar action—all of which have a colchicinic mechanism—act by preventing the retraction of the spindle and, therefore, of the chromosomes, thereby arresting the mitotic process at the metaphase. Some authors have observed a similarity between muscular contraction and spindle retraction on the basis of the biochemical aspects of the two phenomena. Adenosine triphosphate cannot intervene in the process of spindle retraction unless free sulfhydryl groups are present and functionally active.

Some antimitotic drugs, such as the mustard gases, obstruct the cellular division by preventing desoxyribonucleic acid from exerting its effects on the protein syntheses. Some mustard gas derivatives containing oxidized nitrogen are less toxic than the widely used classical mustard gases.

Professor Baserga, of Ferrara, discussed the chemical aspects and therapeutic use of antimitotics. He reviewed the essential concepts about the antimitotics and described the life span of the cells, because this is necessary to an understanding of the effects of the antimitotics. All known antimitotics exert their action by interfering, directly or indirectly, with the cellular biochemistry. Physiological or pathological impairment may follow the use of antimitotics. They are immediate when not linked to the antimitotic action, and they can be classified as local (lesions due to contact with mustard gases) or toxic disturbances resulting from intolerance. Late effects have greater importance and are linked to the antimitotic action that becomes evident not only on cells that are reproducing rapidly and atypically, such as those of neoplastic processes, but also on those of normal organs and tissues that are characterized by a rapid renovation. The same can be said for cells of the intestinal mucosa, marrow, genital organs, and skin.

There may be severe impairment of the hemopoietic organs and the peripheral blood resulting in thrombocytopenia, leukopenia, anemia, and panmyelophthisis. Serious problems, such as the imminent danger of infection, are connected with leukopenia. The red blood cells seem to be more resistant, but this resistance is fictitious, because it is due to the longer life of the red blood cells as compared to that of the white blood cells and the thrombocytes. Germinal cells are very sensitive to the antifolic preparations; in addition to sterility, important mutagenic actions may occur. The antimitotics are no longer limited to the treatment of neoplasms exclusively. High hopes are held for antimitotics still in the experimental stage. Some of these are antinucleic antimetabolites, phosphoramides, the new derivatives of colchicine, and the antifolic acid agents. Prevention of damages caused by the antimitotics is difficult because it is impossible to attenuate their toxic action without interfering with their specific therapeutic action. The therapy can be symptomatic, substitutive (transfusions of blood, bone marrow), specific (dimercaprol [BAL] or metabolites), or stimulating restoration (somatotropic hormone).

Professor Sirtori, of Milan, reported on the possibilities and limitations of the medical treatment of tumors. He defined elective tropism as the activity that a drug has on some diseased organs and tissues and said that one must admit an elective tropism of the mustard gases and polyethylene derivatives for lymphogranulomatous tissue and of urethane for the cells of myeloma and the myeloid cell. Tests to determine the antimitotic activity have great value, and many have already been used in practice. In the field of chemoresistance to the antimitotics, a true chemoresistance must be distinguished from a so-called false chemoresistance. The former is caused by strains that are resistant *ab initio* or by the onset of resistant mutants. The latter occurs when the chemotherapeutic preparation has a cytostatic effect, or when there are in the tumor structures that persist even after cellular lysis.

Professor Piemonte, of Milan, discussed mitotic poisons and ionizing radiations in antiblastic therapy. He omitted the discussion of poisons that cause mutation and of antifolic preparations and reported on new antimitotics such as actinomycin A, which was introduced by Hackmann and used with great success in cases of lymphogranuloma; Haddow and Timmis' myleran to be used exclusively in chronic myelosis; and the latest derivatives of colchicine, which are still in the experimental phase. Podophyllin has been widely used in the local treatment of small cutaneous and mucous carcinomas, but it has not as yet been established whether the results are better than those following radium therapy. Urethane was for some time widely used in the treatment of chronic leukemia and myeloma. Today, however, it has lost much of its value. Greater consideration should be given to mitotic poisons of the mustard gas group, although they are inferior to radiation. Piemonte believes that it is advisable to use radium therapy in cases of lymphogranuloma whether this is confined to one part or involves many parts. Mustard gases are indicated for all phases of the lymphogranuloma in which local or general contraindications prevent the use or the continuation of radium therapy. He believes that a combination of mustard gases and radium therapy, advocated by many, is useless.

Intra-Arterial Therapy.—At a meeting of the "Filippo Pacini" Medical Academy in January, Professor Pratesi emphasized the advantages of giving drugs intra-arterially. The greatest advantage lies in the possibility of bringing the medicament to the impaired part with a minimum of dilution or chemical change. The speaker described the technique used and stressed its simplicity. Among the drugs that can be given in this way are the antibiotics, sympathicolytics, and ganglioplegics. Professor Pratesi has treated over 200 patients with vascular disease in this way at the University of Florence Institute of Medical Pathology. He divides these diseases into three phases—prethrombotic, thrombotic, and post-thrombotic. In the prethrombotic phase, one must consider (1) the inflammatory factor for which synthetic antihistamines of the antistine type are of value; (2) the involutive sclerogenous factor (antistine eventually combined with a ganglioplegic); (3) the vasospastic factor (acetylcholine); (4) the vasodilating factor; and (5) the nervous factor. In the thrombotic phase, an immediate therapeutic intervention with the use of heparin, procaine, and other products followed later by arterioclyses of sodium citrates and sodium chloride is indicated. In the post-thrombotic phase, an attempt to improve the collateral circulation with a treatment similar to that prescribed for the prethrombotic phase is preferable to removing the thrombus by means of trypsin.

On the basis of his experience with patients at the surgical clinic of the University of Parma, Professor Puglionisi discussed the intra-arterial treatment of peripheral obliterating diseases of the arteries. In view of the impossibility of completely checking the course of the disease, the physician should try to slow its progress and relieve the circulatory deficit that is already present. Early surgical intervention permits complete restoration of the circulation in many patients with embolic obliteration, whereas this is possible in only a few patients with chronic obliterations, and the results cannot be considered definitive. Therefore, the treatment is directed mainly against arterial thrombosis in an attempt to prevent it from extending and against ischemia in an attempt to prevent the vitality of the tissues from being impaired. In some instances, because of the presence of certain abnormal factors, such as diabetes or an inflammatory process, special supplementary therapy may be necessary.

Professor Puglionisi said that sympathectomy effects a marked hyperemization, especially on lesions of the lower extremities, with the advantage that it acts only on the diseased area and has a prolonged action. Because many patients are not operated on and a number of operations fail, hyperemization should be carried out by other means. The action of the vasodilating drugs is much more efficacious if the drug is injected into the artery of the area in which its action is needed. At the surgical clinic of Parma, drugs such as nicotinic acid, curare, and eupaverin are used. The intra-arterial injection is followed by a period of stasis applied to the extremity for five minutes, with subdiastolic pressure during the first 40 to 60 seconds and supersystolic pressure during the rest. The hematic factor of thrombosis can be eliminated by giving anticoagulants. This is especially necessary during the period of rapid extension of the thrombotic process, but a maintenance anticoagulant therapy

is useful also in the processes that seem to be already established; this treatment should be individualized to meet the needs of each patient. Intensive anticoagulant therapy may be carried out in some instances by continuous perfusion of heparin into the artery.

Many authors recognize an inflammatory cause of thromboangiitis obliterans with migrating phlebitis. Professor Puglionisi recalled the favorable results obtained after 1940 in many such patients treated by Professor Malan, who injected a 2% solution of acriflavine into the arteries. Because in diabetic patients the treatment of arteritis obliterans requires as its first condition a rigorous control of the diabetes, supplementary intra-arterial injection of insulin is advantageous.

Dr. Conti and co-workers gave hydrocortisone intra-arterially to young patients with endarteritis obliterans. A total dose of 55 mg. caused rapid disappearance of the painful symptoms, quick regression of the inflammatory edema, and the complete cicatrization of the ulcerous area so that the extremity was functionally restored one month after the treatment was begun. The clinical recovery, which was still present six months after the treatment, was accompanied by a slight increase of the oscillometric index and of the oscillatory area of the femoral and tibial arteries. The speakers concluded that in thromboangiitis obliterans hydrocortisone brought directly into the inflamed tissues has an important anti-inflammatory action thereby proving the intimate dysreactive nature of this disease in youth. Intra-arterial injection brings about immediate results with minimal doses of hydrocortisone, whereas the oral and parenteral routes require massive doses and these are often ineffective and cause an imbalance of the glycoactive steroids.

Drs. Pisani and Begattini observed the photoplethysmographic behavior in 25 patients with various peripheral vascular diseases who were treated with various drugs administered intra-arterially. The photoplethysmograms were made before and immediately after the intra-arterial injection, at the beginning, during, and after treatment. The tracings made immediately after the injection revealed in some cases an increased number of oscillations; those made at the beginning and end of the intra-arterial treatment showed only slight photoplethysmographic modifications.

Artificial Hypothermia.—Professor Bobbio discussed the effects of artificial hypothermia in the treatment of shock and in operations on the bloodless heart at the meeting of the Medical Society of Reggio Emilia in December. On exposing animals to progressive cooling, he observed that at a body temperature of about 86 F there is loss of consciousness because of the arrested activity of the cerebral cortex; at about 78.8 F spontaneous respiration is arrested. By prolonging the cooling process and maintaining the animal with artificial respiration, life continues for the higher mammals to a temperature of 64.4 to 68 F. Below these temperatures death from myocardial fibrillation occurs. In the state of hypothermia, there is a marked reduction of the tissues' need for oxygen and consequently a marked reduction of the activity of the heart and circulation, whereas the tissues that are most sensitive to deprivation of oxygen, such as those of the nervous system, become more resistant in the presence of a state of anoxia. Laborit applied the method of artificial hibernation—obtained with cooling and administration of ganglioplegics and antihistamines—to the prevention of postoperative shock secondary to major surgical operations in patients in a very poor general condition. Bigelow studied operations on the bloodless cavities of the heart and demonstrated in dogs the possibility of completely interrupting the circulation in states of hypothermia for 12 to 15 minutes during which operations can be performed on the cavities under direct vision.

Professor Bobbio used artificial hibernation in numerous patients to prevent postoperative shock. The results were satisfactory. He concluded, however, that this treatment should be used only in exceptional cases and mainly for patients whose general condition is very poor. He used artificial hibernation to operate on mammalian hearts that were rendered bloodless by occlusion of the vena cava and the azygos vein. His results confirmed those of Bigelow.

Treatment of Malignant Tumors.—At a meeting of the Lombardy Society of Medical and Biological Sciences, Professor de Gaetani reported on his attempts at chemotherapy and roentgenotherapy for malignant tumors. He studied the influence of aqueous extracts of the spleen and the liver of calf pretreated with carcinogenic hydrocarbons on four patients with malignant neoplasm. This treatment, at times combined with surgery, induced a rapid improvement in the general condition of the patients who, after one year, showed no signs of recurrence or metastasis. He emphasized the fact that this treatment, although nonspecific, may modify the mesenchymal and neuroendocrine disorder characteristic of neoplastic conditions.

The experiments in roentgenotherapy were carried out on six patients with malignant neoplasms who were treated by irradiation of the diencephalon. All the patients showed general improvement and a reduction in the volume of the neoplastic and metastatic masses. In some patients, there was a complete resorption of the neoplastic tissues. Professor de Gaetani assumes the presence of a break in the neuroendocrine equilibrium (beginning in the diencephalon) in the pathogenesis of tumors. This can be stopped by using various means to oppose not only the evolution of the neoplasm but also, and mainly, its production.

MEXICO

Endocrine Disturbances in Malnutrition.—Dr Salvador Zubirán and Dr. Francisco Gomez-Mont of Mexico City have reviewed the pathological, clinical, and functional findings of the thyroid, adrenals, ovaries, testes, and anterior lobe of the pituitary in 526 patients with chronic malnutrition (*Vitamines and Hormones* **11**:97-121, 1953). They concluded that malnutrition produces panhypopituitarism, which is more clearly demonstrated in the gonads. In the testes there is hypospermatogenesis, thickening of the basal membrane, and testicular fibrosis. The excretion of 17-ketosteroids is greatly decreased. The ovarian alterations are characterized by involutionary signs in young women. The clinical findings in both sexes indicated hypogonadism. There were no signs of hyperestrogenism in any of the 245 women, although many with advanced hepatic cirrhosis were included in this group. Hyperestrogenism occurred in 20% of the men. This could not be explained by functional deficit of the liver, because this gland was found to be normal during clinical recuperation, when the liver function tests had begun to show improvement.

In order to clarify the mechanism of these changes, a study of the gonadotrophic function of the hypophysis was carried out. The urinary excretion of pituitary gonadtrophins was found to be frankly diminished in most of the men and the young women and only in 50% of women undergoing menopause. The weekly determination of urinary gonadotrophins demonstrated that the level of pituitary gonadotrophins rapidly increases as the diet is improved. In the young women, this was accompanied by the reestablishment of ovarian function. In the men, the pituitary gonadotrophic increase reaches high levels and is followed by the appearance of estrogens in large quantities. The authors consider that the hyperestrogenism of recuperation in undernourished patients is due to an intense hypophyseal stimulus and not to a defect in hormonal metabolism. Adrenal atrophy was observed in half of the patients. In one of the autopsies it was possible to find hypertrophy of the adrenal cortex. The functional studies showed cortical hypoactivity because the 17-ketosteroid excretion was 3.5 mg. in the men and 2.4 mg. in the women (normal values are 7 to 21 mg. in men and 2.4 to 14 mg. in women). The administration of corticotropin (ACTH) was accompanied by a decrease in circulating eosinophils. The 17-ketosteroid increase was minimal.

It was not possible to identify the clinical manifestations of thyroid insufficiency. The functional tests showed no important abnormalities. The histopathological study showed a low cuboidal epithelium and such study of the anterior lobe of the hypophysis showed signs of atrophy and fibrosis. The authors concluded that there is a secondary panhypopituitarism due to a decrease in the pituitary function. Later studies by the same

authors have helped clarify the mechanisms responsible for this alteration. In April, Dr. Zubirán and co-workers, at the meeting of the American College of Physicians in Chicago, reported that the decreased secretion of the pituitary hormones in the malnourished can be attributed to a difficulty in the liberation of the hormone, as well as to a defect in its synthesis. This view is supported by the fact that women in the menopause, if undernourished, continue secreting large quantities of gonadotrophic hormones. The same type of secretion is seen in young women with pathological destruction of the ovaries or in men with advanced testicular sclerosis. On the other hand the administration of cortisone, or corticotropin, is not accompanied by the usual metabolic changes, especially an increase in the nitrogen secretion. The hypothesis is put forth that in the malnourished patient the hormones are not utilized in the tissues and thus the blood level increases to saturation. This inhibits the pituitary and the secretion of trophic hormones is decreased.

Visit of Dr. Cecil R. Rhoads.—Dr. Cecil R. Rhoads, director of the Memorial Center for Cancer and Allied Diseases and of the Sloan Kettering Institute, New York, visited Mexico in January to explore the possibilities of a joint research project by the Memorial Center and members of the staffs of the Hospital de Enfermedades de la Nutrición, Mexico City, and of the Unit of Cancerology of the Hospital General, Mexico City.

TURKEY

Puerperal Encephalitis.—In *Dirim*, vol. 28, no. 2, Dr. Ö. Dürüshken of Istanbul described a case of encephalitis caused by puerperal septicemia. A 28-year-old woman complained of disturbed vision, dysphagia, and loss of balance. Two weeks earlier she had had a normal delivery shortly after which her legs became edematous. Urinalysis revealed albumin. Her blood pressure was 180/80 mm. Hg. On admission to the hospital, her temperature was 100.4 F; her pulse rate was 90; and her blood pressure was 130/80. She had lateral and vertical nystagmus in both eyes; her liver had descended below the costal margin; her spleen was palpable; she complained of vertigo; and there was anuria. Laboratory examination showed a sedimentation rate of 40 mm. after one hour. The blood cell count revealed 3,160,000 erythrocytes and 6,000 leukocytes; and the hemoglobin level was 80%. Pelvic examination was negative. A diagnosis of puerperal infection was made, and the patient was given 1 million units of penicillin. On the following day, she was comatose, she had a right facial paresis and paresis of the left arm and leg, cerebellar dysmetria, diadochokinesia, and left hypotonia, and her tendon, bone, pharyngeal and palative reflexes were absent. The Babinski reflex was present. Examination of her spinal fluid revealed 30 mg. of albumin per 100 cc., 29 mg. of glucose per 100 cc., and lymphocytosis. Urinalysis revealed traces of albumin; microscopic examination of the sediment revealed a few leukocytes and erythrocytes. The patient was given calcium therapy and complete rest. Within seven days the coma, facial paresis, and dysphagia disappeared, and the patient's general condition improved. On the 15th day, phlebitis occurred in the left leg and the leg was immobilized. The prothrombin time determined at three day intervals was 18.5, 26, and 37.7 seconds, respectively. After the administration of vitamin K and calcium, the prothrombin time returned to normal. After a long and complete rest, the patient recovered. During her illness, she received 9 million units of penicillin, 8 gm. of streptomycin, 6 gm. of a sulfonamide, 1.2 gm. of vitamin B_1, 100 cc. of hypertonic dextrose solution, 17 gm. of calcium, 1.5 gm. of vitamin C, 3 gm. of Cylotropin (a mixture of methamine and sodium salicylate) and ethyl biscoumacetate (Tromexan ethyl acetate). Ophthalmologic examination revealed normal eye grounds and normal vision and that the nystagmus was the result of pyramidal irritation. The patient was discharged from the hospital.

Hookworm.—In the *Turkish Bulletin of Hygiene and Experimental Biology*, vol. 13, no. 2, 1953, Dr. Kemal Özsan has reported the results of hookworm screening study in the eastern coastal regions of the Black Sea in 1946. The presence of Necator americanus in Turkey was first recognized in 1920. The patients were all natives of the eastern Black Sea coast. In 1924, the health department of the new Turkish republic instituted a survey that revealed that the whole farm population along the eastern Black Sea littoral was infested with hookworm. In 1929, Dr. Ziya Öktem initiated a hookworm campaign. He reported that the species in question was N. americanus, that 40 to 50% of the rural population was infested with the parasites, that 5 to 15% of the population further inland had become infected during temporary employment in the coastal regions, and that the topography and climate of the Black Sea coast, though in the temperate zone, are favorable to the development of the larvas. It is very hot in the summer and even then cloudy, foggy, and extremely humid. An abundance of trees and shrubbery prevents the sun from reaching the soil. Not far inland are mountain ranges 3,500 to 4,000 m. high, and dense forests prevent air currents. During the three and a half years that Professor Öktem directed the campaign around Hopa, Pazar, and Rize in 172 villages, 21,949 stool specimens were examined and more than 39,000 persons were given carbon tetrachloride. Patients were given 0.1 gm. of carbon tetrachloride per year of age. There have been no side-effects. After one dose, the incidence dropped from 49.5 to 17%. Of 226 positive carriers, 195 became negative after a second dose.

Dr. Özsan's investigation began in 1946 and comprised 14 rural communities in the eastern Black Sea littoral with a population of 159,980. A total of 77,619 stool specimens of which 23,152 (30%) were positive were examined. From 80 to 90% of the population harbored ascarides. The hookworm incidence was higher in the villages situated in the narrow valleys through which rivers flow; in the higher drier regions it was much lower. Previous investigations revealed that, commencing at the Russian border, a large proportion of the farm population in the environs of the cities and towns of Hopa, Rize, Trabzon, Giresun, and Ordu was infested with hookworm disease. Patients in hospitals of the western Black Sea coast from Samsun to Istanbul, or patients in Istanbul, Ankara, Izmir, or Anatolian hospitals, found to be infected with N. americanus invariably are natives of the eastern Black Sea coast. It is believed that Chinese coolies, who during World War I were working on military roads for the Russians who then occupied that area, propagated the disease. Dr. Özsan concludes that, though the use of human excreta for fertilizing has been prohibited, it is still being used, and as long as the farmers, who in that region are very poor, are not supplied with sufficient artificial fertilizer, health education and other measures will not greatly affect the incidence, let alone suppress the disease.

Postvaccinal Allergy.—In the *Turkish Bulletin of Hygiene and Experimental Biology*, vol. 13, no. 2, 1953, Dr. Niyazi Musa Erzin reported his observations on BCG vaccination, postvaccinal allergy, and local reactions. Dr. Erzin, who is director of the Ankara Refik Saydam Institute of Hygiene, where the vaccine is prepared, organized and supervised the BCG campaign. Retests 8 to 12 weeks after interdermal vaccination on 2,959 persons, the school population, and adults in urban and rural communities of Edirne, Kirklareli, Babaeski, and Lüleburgaz, all in Trakya, Turkey's European province, and among two Izmir counties and schools, made by two experts from the World Health Organization, revealed a tuberculin conversion rate of 97.8 to 99%. Investigation in nine rural communities of Ankara by Dr. Erzin's associate Dr. Daver Özlüarda 10 to 15 weeks after vaccination revealed a conversion rate of 99.8% in 711 persons. Five Mantoux units were used to determine the local reaction 8 to 14 weeks after interdermal vaccination. Of 3,670 persons, 41 (1.12%) had negative reactions with an induration of 0 to 4 mm.; 752 persons (20.5%) had positive reactions with 5 to 10 mm. induration; 1,990 persons (54.5%) had 11 to 15 mm. induration; 809 persons (22%) had 16 to 20 mm. induration; and 78 persons had more than 20 mm. induration. To determine the duration of allergy, Dr. Özlüarda made second retests on 638 persons in seven rural communities of Ankara 22 to 25 weeks after vaccination using five Mantoux units. These revealed an average tuberculin conversion of 97.7%. Absence of local reactions was rarely observed. Infiltration was usually 10 to 15 mm.; under 10 mm. in 25%; and 16 to 20 mm. infiltration with ulceration and crust formation was observed in 2% of the vaccinated children. Local reactions lasted from 6 to 9 months and in some cases 12 months. Swelling of regional lymph nodes was observed in 2%.

CORRESPONDENCE

MALIGNANCY IN NODULAR GOITER

To the Editor:—I am dismayed at the inconsistencies in the article in THE JOURNAL, April 17, 1954, page 1321, by Joseph Sokal concerning the incidence of malignancy in toxic and nontoxic nodular goiter. On page 1322 is the statement that "Thyroid nodules are premalignant lesions." This is the accepted opinion of the majority interested in thyroid disease, and because of this fact surgical removal is advised. Yet in the summary on page 1325, it is stated: "The risk of cancer is small in all types of goiter. About 1% of toxic nodular goiters are malignant. The incidence of cancer among unselected nontoxic . . . goiter is probably less than 0.2%." The inference here is that one need not worry that cancer will arise in goiter because the estimate of the author is so low. Yet the fallacy of this reasoning and the false sense of security it engenders is adequately borne out by the case report the author presents in which the patient "was first seen . . . in 1927. . . . Moderate enlargement of the right lobe of the thyroid was noted . . . and two firm nodules were described. . . ." Evidently surgery was not recommended at this time. The man was seen again in 1931 and 1938, and it was not until 1938 that the advisability of surgery was mentioned. "He was next seen in 1940, after several weeks of more rapid growth of the goiter and after the appearance of nodes on both sides of the neck." "There was extension behind the sternocleidomastoid and into the mediastinum." "On microscopic examination the thyroid was found to be completely replaced by carcinoma. . . ." If surgery had been performed in 1927, when the enlargement of the right lobe of the thyroid and the two firm nodules were first described, the patient probably would never have developed thyroid cancer. If, as Dr. Sokal states, "Thyroid nodules are premalignant lesions," then the time for surgical treatment is during the premalignant stage, not several years later when "There was extension behind the sternocleidomastoid and into the mediastinum" and "the appearance of nodes on both sides of the neck." It is useless to lock the stable door after the horse has been stolen. In the routine removal of thyroid nodules, there should be no mortality in the hands of an experienced thyroid surgeon and the patients are discharged from the hospital on the third or fourth postoperative day.

I recently removed thyroid nodules in three consecutive patients seeking medical care for other complaints. All of these nodules were malignant. A fourth patient had a recurrent thyroid nodule two years after excision and was advised by his family physician to delay operation for nine months. When removed, the microscopic diagnosis of the nodule was carcinoma metastatic to three lymph nodes. In thyroid cancer, an ounce of prevention is worth a pound of cure, and all thyroid nodules should be removed surgically.

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Dr. Trevor's letter was referred to Dr. Sokal, whose comment follows:

I used the term premalignant in the same sense as Levin (*Cancer* **1**:489, 1948), who pointed out that "The concept of a 'precancerous' lesion is essentially a statistical one, since it indicates an increased probability of developing cancer." This is a simple and useful definition that is appropriate to the present state of our understanding of the pathogenesis of cancer. Thyroid nodules are premalignant lesions because thyroid cancer occurs much more frequently among persons with nodular goiter than among those without goiter. However, even among persons with nodular goiter, the risk is not very great. A somewhat similar situation exists in the case of most premalignant lesions. Only a minority of rectal polyps become malignant; the usual course of leukoplakia and of senile keratosis is benign; and there are many hundreds of nevi that cause no trouble for every one that gives rise to melanoma. Classification of a lesion as premalignant does not of itself constitute an indication for surgery.

The purpose of my paper was to call attention to some common misconceptions and to indicate an order of magnitude for the risk of malignant change in a completely unselected population with nodular goiter. I think it desirable that correct statistics be available to physicians who have to deal with this difficult problem. I do not suggest that the decision in any individual case be based solely on my analysis of probabilities in a large population. It would be just as wrong to say that my figures prove that no goiter should be removed, as to claim that someone else's figures prove that all goiters should be extirpated. Some nodular goiters are dangerous. In my case 1, the lesion described was recognized as such, and thyroidectomy was strongly recommended at a time when the goiter was presumably benign. As was stated in the case report, the patient refused surgery.

The question of prophylactic surgery in nodular goiter is a very complex one. I did not discuss it in my paper and I cannot do so in this brief space. However, I agree with Crile (*J. A. M. A.* **139**:1247 [April 30] 1949) that nonselective removal of all thyroid nodules is not desirable. Operations on the thyroid, even in the hands of experienced surgeons, are associated with a small but measurable mortality and an appreciable morbidity. Furthermore, such operations do not eliminate the risk of cancer. Dr. Trevor offers an example of this in the description of his patient in whom cancer developed two years after excision of a thyroid nodule. Such cases are not rare. Hertz (*Am. J. Roentgenol.* **46**:474, 1941) cites instances of patients who have had as many as four prophylactic operations for nodular goiter, but in whom thyroid cancer developed anyway.

TONSILS AND BULBAR POLIOMYELITIS

To the Editor:—In the April 3, 1954, issue of THE JOURNAL there was an editorial entitled "Relation of Absence of Tonsils to Bulbar Poliomyelitis." It was based largely on a statistical study by Weinstein, Vogel, and Weinstein (*J. Pediat.* **44**:14 [Jan.] 1954). These authors inferred that the absence of tonsils and adenoids increased susceptibility to the development of bulbar and bulbospinal poliomyelitis. The validity of the statistical study is not questioned, but in this, as in many other recent similar reports, the conclusion reached is on somewhat fallacious grounds.

The fallacy is that the incidence and severity of a given disease are being compared in two biologically and immunologically dissimilar groups of persons. In general the group not having had tonsillectomy has had better immunity to disease, especially in the upper respiratory area and hence has not been subjected to tonsillectomy. The second group, on the other hand, has been subjected to tonsillectomy because of poor immunity to disease, particularly in the cephalic area. This poor immunologic response would undoubtedly also apply to invasion by the poliomyelitis virus. It is my clinical impression that there is usually a greater degree of autonomic instability in the cephalic area in these persons before tonsillectomy and that as a result the area may have become "conditioned" to respond in an abnormal manner to many forms of stress, probably including that of poliomyelitis virus invasion. The unanswered question still is whether the higher incidence of bulbar poliomyelitis in patients who have had tonsillectomy is the result of the absence of the tonsils and adenoids per se or the result of preexisting, greater local susceptibility to the poliomyelitis virus as compared to that of patients who have not had tonsillectomy.

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MISCELLANY

STORIES ON STONE

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A chronicle of strange and curious sicknesses and an informal record of the progress of medicine in America may be found in the epitaphs on the tombstones in many old graveyards. In "Stories on Stone: A Book of American Epitaphs," published by the Oxford University Press, are reproduced many tombstone inscriptions of significance to the medical historian. These are included in a chapter titled "Doctors and Patients."

"Stories on Stone," the first comprehensive publication of American epitaphs, contains more than 750 verified inscriptions from all states and representing each decade in American history. Among the inscriptions of particular interest to the medical profession are the following, which are reprinted by permission of the publisher.

Statistical matter is offered in the epitaph to Benjamin Rowe, whose gravestone is found in Old Cemetery, Kensington, N. H.

> In memory of Benjamin Rowe
> Esq. who after a life of great
> usefullness & Patiently enduring 4
> Years Illness with a Dropsy, underwent
> the operation of Tapping 67 times, from
> his Body was drawn 2385 pounds
> of Water quietly Departed this Life
> the 28 Day of March, Anno Domini
> 1790 in the 71st. Year of His Age.

This epitaph from St. Thomas Episcopal Church, Bath, N. C., was given prominence when Edna Ferber included it, with only a change of name and place, in her novel "Show Boat" (1926):

> Here lyes the body of Mrs: Margaret Palmer,
> wife of Robert Palmer, Esqr: one of His
> Majestys Council & Surveyor General of the
> Lands of this Province, who departed this
> life Octr 19th 1765. Aged 44 Years. After
> labouring ten of them under the severest
> Bodily Afflictions brought on by Change of
> Climate and tho' She went to her Native
> Land receiv'd no relief but return'd & bore
> them with uncommon Resolution and Resignation
> to the last.

In the old graveyard near the Unitarian Church, Barnstable, Mass., are stones to a doctor and his wife. The front of the doctor's monument indicates the pride of ancestry:

> Dr. Thomas Wd Fossett
> Born 1813
> 9th son of Obil
> and
> Grandson of John Fossett
> and
> Great, great, great grandson
> of Patrick of Ireland
> John's mother was Scotch
> I am over 80 years of age.

On the reverse side is his record in medicine:

> I have practiced the eclectic system
> in Mass., Ohio and Mich., for over 50 years
> and have never lost that number of patients.

The inscription on the stone of Emily Fossett, died 1885, aged 72, reads:

> Here lies my body
> Mouldering to clay
> But the spirit has
> Flown to the realms of day,
> Where all can dwell
> in peace and love
> In the beautiful city
> The fair courts above.
> I conversed with the spirits
> of the dead for
> forty years, as with the living.

In the Old School Baptist churchyard, near Roxbury, N. Y., is a stone listing the children of Timothy and Eleanor Corbin. The death of David in 1839 at the age of 1 year is explained in this manner:

> His death was produced by being spured in
> the head by a rooster.

An epitaph in Girard, Pa., comments:

> Ellen Shannon
> Age 26 years
> Died March 21st 1870
> by the explosion of a lamp
> filled with R. E. Danforth's
> non-explosive fluid.

A 19th century explanation of lightning is given on a tombstone on Burial Hill, Plymouth, Mass.

> Bathsheba James, wife of Capt. William Holmes
> Mariner and daughter to Capt. Joseph Doten Do.
> She was kill'd instantaneously in a Thunder
> storm by the Electrich fluid of lightning on
> the 6th of July, 1830, aged 35 years and 26 days.

A bitter denunciation of the medical profession is found on the grave slab of Ruth Sprague, died 1816, aged 9, in Maple Grove Cemetery, Hoosick Falls, N. Y. After the girl's burial, Roderick R. Clow, a student, exhumed the body and removed it to a local laboratory for study. When the remains were recovered the following words were inscribed on the stone:

> She was stolen from the grave
> by Roderick R. Clow & dissect-
> ed at Dr. P. M. Armstrong's office
> in Hoosick, N. Y. from which place
> her mutilated remains were
> obtained & deposited here.
> Her body dissected by fiendish Men
> Her bones anatomised,
> Her soul we trust has risen to God
> Where few physicians rise.

On the grave of Frances Cerny, died 1902, aged 6, in St. Mary's Cemetery, Winona, Minn., is this indignant sentiment:

> Killed by an unskilled Dr.

A congenial doctor of Pawtucket, R. I., long in the habit of accepting the meal check at a local drug store where he and friends congregated, inscribed a large boulder, now marking his grave in Oak Grove Cemetery, as follows:

> William P. Rothwell M. D.
> 1866-1939
> This is on me ℞

The laconic epitaph to Dr. Fred Roberts, died 1931, aged 56, in Pine Log Cemetery, Brookland, Ark., reads:

> Office up stairs.

MEDICAL FILM REVIEWS

You're the Doctor: 16 mm., black and white, sound, showing time 19 minutes. Produced in 1951 by Audio Productions, New York, for and procurable on loan ($4.00) or purchase ($35.00) from the American Hospital Association, 18 E. Division St., Chicago 10.

This film portrays the indispensable role of the voluntary hospital in safeguarding the health of the community. Many of the "behind the scenes" functions of the hospital—the scientific laboratories, the various other specialized departments, and the intricate and costly equipment, which help make American hospitals the finest in the world—are authentically portrayed, and their vital part in diagnosis and treatment are illustrated. The film dramatically shows how one patient discovers that his

hospital is an investment in health. This film shows very well the operation of a hospital. It is well organized, and the photography and narration are excellent. It is recommended for service clubs and other lay groups and would be especially useful at the time of a fund-raising campaign. Although not primarily intended for recruitment, it could be used in this connection for nurses and other hospital personnel.

THE LEISURE CORNER

CANINE COMPANIONS

At the very moment the first wild dog cautiously accepted man as a friend, a cordial relationship was inaugurated between biped and quadruped that has persisted for hundreds of generations. Just when the association or partnership of man and dog began and how it was brought about is vague. Perhaps it was due to the offering of a morsel of food by a youthful cave dweller, or perhaps it happened when some kindly cave-woman took compassion on an orphaned puppy or litter of puppies and nursed them along into maturity as playthings for her own children. Certain it is, however, that as a result of a blending of interests the dog has been able to impress his personality slowly

Boston terrier.

and surely on human mores and habits. On the one hand, the dog has adjusted himself to man's whims; on the other, man has developed criteria, rules, and regulations to protect the canine population.

In a certain sense the dog mirrors man, and man has used his four-legged companion to symbolize various human characteristics—hence the expressions "gay dog," "dogged resistance," "hangdog expression," and so on. Man has often esteemed the dog to be second only to himself; he has at times actually regarded the dog as an equal and even as an object of worship. Nor has dog betrayed the confidence of his two-legged companion, for he has repeatedly demonstrated his ability as an unrivalled ally, whether as a guard of man's possessions, a hunter, a playmate, or an aide in war and peace. Indeed, the dog is a versatile creature—as brave as a lion, as gentle as a kitten, capable of doing tricks with almost human skill or displaying exasperating stupidity, attacking a ferocious beast on one occasion and running from his own shadow on the next. He will follow the track of his prey relentlessly, then fruitlessly chase his own tail. Courageous and loyal, dogs are also indisputably versatile animals, with a pronounced ability for meeting almost any condition imposed on them. Because of both instinct and training, every breed fits into some niche of present-day life; however, despite the claims of more enthusiastic dog fanciers, dogdom is not represented by a true "jack-of-all-trades." While a dog exists for almost every purpose, there is no dog suitable for all purposes.

In all probability the first use to which the dog was put by man was that of a hunting companion. Even now, a larger number of dogs are probably kept for this purpose than for any other. In the hunting of nearly every species of game on the North American continent, at least one breed of dogs might well be called specialists. Specialization in the canine kingdom is produced by training, development of certain physical characteristics, and the natural inclinations of individual breeds.

One of the oldest instincts inherent in a dog is that of guarding his master's person and property. Once a dog has accepted either a person or a family as master, he quickly develops a well-defined sense of proprietorship and the readiness to defend his master's person, privacy, or property against all intruders. This sense of possession and guardianship is found in virtually all breeds of dogs, although it asserts itself more often in bolder, more aggressive breeds. Although these qualities are attractive, the most outstanding attribute of the dog is his alliance with man—his steadfast companionship; neither whys nor wherefores exist to weaken the link of friendship between owner and owned. It matters little to a dog whether his master is rich or poor in the world's goods, or even forsaken by his fellow man.

Regardless of the purpose for which a dog is chosen by a physician or his family, it is probably best that the animal be a pure-bred dog. It costs no more to maintain a pure-bred dog than a mongrel, and the advantages of the former are many. Of course, many smart dogs are mongrels, but unfortunately they are unable to reproduce their virtues reliably. Once a selection has been made of a specific breed, it is best to deal with a reliable and established breeder or a dealer who has a good reputation. Do not look for a bargain—bargains really do not exist. Cheap or bargain puppies are expensive in the long run, for they generally have some fault that may not be immediately apparent.

In selecting a dog for city living, the physician should carefully consider the needs of his family as well as the household environment. Obviously, breeds such as the St. Bernard, great Dane, and Newfoundland are out of place in a city apartment, for these large dogs require a great deal of room. Smaller breeds ordinarily meet the needs of physicians and their families; any of the smaller breeds make fine city dogs. While terriers are generally the most active of the lot, several of the terrier breeds are inclined to be placid. The Boston terrier, a distinctly American creation in the canine world, is active, alert, and affectionate, with a handsome appearance and winning ways. Other popular house dogs are the cocker spaniel, the dachshund, the wire-haired fox terrier, the Scottie, the Cairn, and the Sealyham. It must be borne in mind that the terriers are active little dogs, especially fond of the outdoors.

Physicians living in suburban or small-town homes have the advantage of being able to select from a greater variety of breeds than their city-dwelling colleagues. Virtually all dogs thrive happily in suburban environs; the choice of a breed is mostly a matter of taste. Good all-around canine companions include the collie, the Shetland sheepdog, and the Dalmatian; still others are the popular beagle, the boxer, the poodle, and the English springer spaniel. The setters—English, Irish, and Gordon—make good family dogs, as do most of the retrievers, while the pointer is happiest when used for hunting and allowed considerable freedom. Large breeds such as the great Dane, greyhound, wolfhound, and mastiff are more suitable for large estates. Small children left on their own can hardly be expected to handle these breeds properly.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

First Results of 1-Hydrazinophthalazine in Patients with Arterial Hypertension. P. C. Feraboli. Minerva med. **45:**413-416 (Feb. 10) 1954. (In Italian.)

Thirty-six patients with essential or arteriosclerotic hypertension were given hydralazine (Apresoline). Some of them were hospitalized; others were treated on an ambulatory basis. The oral route was used, the drug was given to the patients on a full stomach, and the therapy was continued in some instances for as long as three months. The optimal daily dose was found to be from 100 to 150 mg. in two or three divided doses. The drug did not cause toxic effects, but its use had to be discontinued in five patients who did not tolerate it. The hypotensive effect of hydralazine became evident in many patients. There was an average drop of 29 mm. Hg in the systolic and 11.6 mm. Hg in the diastolic pressure. The albuminuria that had been present in some patients disappeared within a few days; headache, dizziness, and insomnia were decreased; and pain was attenuated in the patients in whom spasm of the coronary arteries was present. There were no electrocardiographic changes in those who were observed for several months. Good results were obtained in 11 patients; there was improvement in 10; the condition remained unchanged in 6; the drug was not tolerated by 5; and in 4 the arterial pressure returned to the initial values as soon as the therapy was discontinued. Although the effect of hydralazine is not constant, this drug does have the characteristics of hypotension-inducing drugs, and it increases the renal blood flow without altering the volume and viscosity of the blood and without impairing the myocardium.

Studies on Diffusion in the Body Fluids of Isonicotinic Acid Hydrazide: Application to Treatment of Tuberculous Meningitis. A. Ravina, M. Pestel and R. Thielen. Presse méd. **62:** 417-419 (March 17) 1954. (In French.)

The diffusion of isoniazid (isonicotinic acid hydrazide) in the blood and the cerebrospinal fluid was studied, and it was found that significant amounts of the drug circulated in these fluids after oral or rectal administration. Eight patients with tuberculous meningitis were successfully treated by this method. No relapses were observed in a follow-up of from three months to two years. The simplicity of the technique constitutes its great advantage over intrathecal injection. It is hoped that this advance will realize the same progress in the treatment of tuberculous meningitis as it did in purulent meningitis.

Oral Treatment of Pernicious Anemia with Intrinsic Factor Concentrate and Vitamin B_{12}. C. P. Lowther, W. D. Alexander and E. B. Hendry. Lancet **1:**495-497 (March 6) 1954.

Lowther and associates are concerned with Bifacton, a preparation consisting of Castle's intrinsic factor in association with vitamin B_{12}. This preparation is produced in tablet form for oral administration. Their aim was to ascertain whether this preparation would maintain patients with proved cases of pernicious anemia in full hematological and neurological remission. Twenty patients who have now been so maintained for six months are reported on in this paper. They included 8 men and 12 women. In all of them, megaloblastic marrow reaction, histamine-fast achlorhydria, and the characteristic picture of the peripheral blood had been found, and initial treatment had produced the expected reticulocytosis. Three patients had subacute, combined degeneration of the cord; one had active pulmonary tuberculosis and throughout the six months of the experiment was treated with streptomycin and *p*-aminosalicylic acid. The patients had been treated with either vitamin B_{12} or a refined liver extract for different periods before all the injections were stopped and treatment with Bifacton was begun. No evidence of hematological or neurological relapse was seen after six months' continuous treatment with these tablets. For this length of time at least. Bifacton provided adequate treatment for pernicious anemia.

Renal Osteodystrophy. G. Argil. Medicina. **34:**97-101 (March 10) 1954. (In Spanish.)

The author reports on seven cases of renal osteodystrophy. The disease is due to disturbed acid-base balance from prolonged renal insufficiency in early childhood. The renal disorder may originate in congenital abnormalities of the kidney, chronic nephropathy in early infancy, malnutrition in early childhood, and hypophysial insufficiency. As a rule the disease is first observed by the parents when the patient, at the age of 7 or 9 years, is short and puny for his age. The changes of the bones include widening of the epiphyses, softening of the diaphyses, and curvatures and other deformities. The characteristic rachitic rosary is present in all cases. The bones are soft and fragile. Fractures with incomplete consolidation are frequent. The legs assume the form of K or of X, because of unilateral or bilateral genu valgum or genu varum, often with pes valgus or pes varus. The bones, on roentgen examination, show extensive zones of osteoporosis. The patients are either slightly subnormal or nearly dwarfs. The younger the patient when the renal disorder starts the more marked the deformities of the bones. The renal symptoms are varied. In all cases there are albuminuria and diminished excretion of phenolsulfonphthalein. Cylindruria is frequent. Primary and secondary sexual characteristics appear very late. The intelligence of the patients is normal. The clinical diagnosis may be confirmed by urography with demonstration of congenital malformations of the kidney or pathological changes of the structures. The prognosis is grave. The disease, without treatment, progresses to advanced stages with fatal uremia or fatal intercurrent infection. The treatment aims to correct the chronic renal disorder. Treatment of classic rickets is of no avail. Ultraviolet rays and vitamin D have not been found to be of value. Orthopedic treatment for correction of deformities is contraindicated. In two out of the seven cases observed by the author, satisfactory results were obtained from administration of hypophysial hormones. The patients gained in stature and in growth. Kidney function improved. The deformities of the bones remained unchanged. The author advises administration of thyroid hormones to patients with the disease and testosterone to somewhat older patients.

Proctitis Venenata. M. M. Marks. Proctology **18:**117 (Sept.) 1953.

Marks calls attention to a proctologic symptom complex that he designates as popcorn proctitis. Patients present themselves with the complaint of recent bleeding at stool, with or without pain. Proctologic examination shows discrete, superficial, linear lacerations of the rectal mucosa and/or fissuring of the anal integument with sphincter spasm. Further questioning brings evidence that popcorn has been eaten recently. Roasted corn, unless well masticated when eaten, leaves an indigestible portion of the kernel sufficiently large and pointed to lacerate the bowel wall when imbedded in a bolus of firm stool. The mucosal lesions will heal without treatment, providing roughage and

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highly seasoned food are eliminated from the diet for a week. Painful anal wounds are best treated with bland anesthetic ointments and daily gentle finger dilation by the patient himself or at intervals by the physician. In adults, popcorn proctitis may reactivate previously existing anorectal disease. The resulting lesions, such as cryptitis, abscesses, anal ulcers, and bleeding from lacerated hemorrhoids, may require surgical correction. In children, the symptoms of bleeding after eating corn are usually self-limiting.

Gamma Globulin in Prevention of Infectious Hepatitis: Studies on Use of Small Doses in Family Outbreaks. D. Y. Y. Hsia, M. Lonsway Jr. and S. S. Gellis. New England J. Med. **250:**417-419 (March 11) 1954.

Hsia and associates say that in previous studies carried out by their group on infectious hepatitis a high incidence of secondary cases was seen in families. Secondary cases appeared in 14 of 29 families in which gamma globulin was not administered to the contacts. Among these, hepatitis with jaundice subsequently occurred in 18 of 51 exposed children. In contrast, only one case of infectious hepatitis developed among the 33 adults and 22 children who were exposed but who had been given 0.1 cc. of gamma globulin per pound of body weight. The present report is a continuation of the initial study on family outbreaks of infectious hepatitis using a smaller dosage of gamma globulin, namely 0.01 cc. per pound of body weight. Gamma globulin in this dosage was given to alternate members of 40 families, in each of which a sporadic case of infectious hepatitis had developed. Only one case of hepatitis occurred among 38 exposed adults and 57 exposed children who were given gamma globulin. Jaundice was noted six days after injection in that case. In comparison secondary cases appeared in 2 of the 55 exposed adults and 11 of 40 exposed children who were the untreated controls within the same families. Administration of 0.01 cc. of gamma globulin per pound of body weight thus appears to be as effective as that of 0.1 cc. in preventing the spread of infectious hepatitis within family groups.

Results of Methonium Treatment of Hypertensive Patients: Based on 250 Cases Treated for Periods up to 3½ Years, Including 28 with Malignant Hypertension. F. H. Smirk. Brit. M. J. **1:**717-723 (March 27) 1954.

There is clear evidence that the prognosis of malignant hypertension is much improved by effective control over the blood pressure level through the administration of methonium salts. Of the 28 malignant hypertensive patients so treated by the author, including 7 with renal insufficiency or advanced heart failure, 21 were living and 7 were dead at the time of writing. The average survival time of those who died was 9.7 months and of those who lived 22.8 months. A considerable majority of the survivors returned to productive lives, the men working at their previous occupations and the women doing housework. In hypertensive patients with retinal lesions grades 2 and 3 taken together, the mortality figures were better in 122 treated cases (16.4%) than in 53 controls (28.2%), but no claim of statistical significance is made. Objective improvements included (1) the disappearance in most cases of such changes as papilledema, retinal edema, soft exudates, hemorrhages, and, after long treatment, star-shaped macular figures; (2) return to work of most patients under 60 with malignant hypertension, cardiac asthma, or congestive heart failure, including in most cases the elimination of the use of digitalis, mersalyl, or substantial salt restriction; and (3) electrocardiographic improvement and tendency to decrease of heart size. The consistency with which these results have been produced during three and a half years leads the author to state that less satisfactory degrees of improvement are usually due to inadequacy of the regimen used. In a minority of patients, the doses of methonium salts that relieve hypertensive manifestations led to much discomfort from side-effects; methods of alleviation that helped some patients are suggested.

The Pathogenesis of Rheumatic Fever. D. A. Long. Lancet **1:**529-537 (March 13) 1954.

Long reviews the natural history of rheumatic fever and selects for study the influence of nutrition and of hormones on the disease. He suggests that hemolytic streptococci cause rheumatic fever, that streptococcic allergens and toxins act synergistically on mesenchymal cells to produce the rheumatic syndrome in susceptible persons, and that the response to streptococcic allergens is of the type seen with tuberculin, not of the type seen in anaphylaxis. The hypothesis is advanced that susceptibility to rheumatic fever and sensitivity to bacterial allergens amount to the same thing. The rheumatic fever patient and the BCG infected guinea pig are alike (1) in showing bacterial allergy of the tuberculin type, (2) in their inability to synthesize ascorbic acid, (3) in their response to cortisone, and (4) in that their susceptibility is decreased by diabetogenic agents and increased by antidiabetogenic agents and by hyperthyroidism and hypothyroidism. In the guinea pig, sulfhydryl compounds, such as reduced glutathione, increase sensitivity to tuberculin; conversely, factors that decrease the nonprotein sulfhydryl content of the tissues diminish sensitivity to tuberculin. Since the responses of rheumatic persons and of the tuberculin-sensitive guinea pigs resemble each other in many ways, it is possible that effects similar to these might be obtained in human beings. There is a profound species difference in response to cortisone. Man, monkey, and guinea pig are resistant and the rat, mouse, rabbit, and ferret are sensitive to its action. Clinical and experimental evidence suggest that the concept of the adaptation syndrome is based on a false analogy and may be misleading when applied to man. Cortisone does not exert a nonspecific anti-inflammatory (antiphlogistic) action in the skin of the guinea pig; it is without effect on acute allergic phenomena but depresses sensitivity to delayed allergic responses of the tuberculin type. Cortisone protects guinea pig skin from the toxic products liberated by the union of tuberculin antibody and allergen. There is evidence supporting the hypothesis that cortisone decreases cell permeability, thus reducing the size of the lesion by preventing the outflow of toxic substances from the damaged cells. It is unlikely that cortisone exerts this anti-allergic activity by inducing changes in antibody or by interfering with the union of antibody and allergen. The desensitizing effect of cortisone is indirect. Cortisone antagonizes protein in general and methionine in particular to facilitate desensitization by ascorbic acid, but desensitization is more closely linked with carbohydrate than with protein metabolism.

Observations on Brucella Species Based on Examination of 800 Strains. J. C. Cruickshank. J. Hyg. **52:**105-118 (March) 1954.

During the last seven years 800 strains of Brucella were submitted to the Brucella Reference Laboratory in London for identification. Most of the strains were submitted from the laboratories of the Public Health Laboratory Service. Many of these were strains about which an opinion was requested because they had given some unusual reaction. Some bacteriologists sent in all the strains they had isolated, thus providing a useful cross section of the types occurring in their particular areas. Most of the strains were isolated from milk in Great Britain, but strains from other countries and from cases of brucellosis were also examined. Of 738 strains from milk in Britain, 680 were Brucella abortus, of which 62 (9.1%) were of a type inhibited by all the usual test dyes in their customary concentrations. Thirty strains of Brucella melitensis, behaving typically in all laboratory tests, were obtained from milk from individual cows, herds, or bulk sources. Br. melitensis has now been identified from 24 separate farms and one tuberculin tested bulk supply in Britain. Eighteen strains behaved like Br. abortus in biochemical tests, but serologically like Br. melitensis. Of the relatively small number of strains isolated from patients with brucellosis in Britain, all those from persons infected in Britain were Br. abortus, with the exception of two laboratory infections with Br. melitensis. The organisms isolated in Britain from patients infected abroad comprised three strains of Br. melitensis, one strain behaving biochemically like Br. abortus and serologically like Br. melitensis and two behaving biochemically like Br. melitensis and serologically like Br. abortus. One of the latter was from a patient infected in southern Italy, and

the examination of 19 strains from that country showed that 13 were of this type. The thionin-resistant type of Br. abortus was identified several times, from cases of brucellosis in Rhodesia, Kenya, and Italy. No strains of Brucella suis were observed.

Desoxycorticosterone Acetate Therapy of Rheumatic Diseases as a Problem in Dosage. G. Wittlinger and L. Lange. Endokrinologie **31**:70-78 (No. 1 & 2) 1954. (In German.)

The use of corticotropin and cortisone in rheumatic disease involves not only the problem of scarcity and high price of these hormones, but also undesirable secondary effects. Wittlinger and Lange used desoxycorticosterone acetate. The histories of patients treated with desoxycorticosterone acetate indicate that the effect of this drug in rheumatic disorders is largely determined by the size of the dose. Prolonged remissions were obtained when small doses were given over long periods. The application of large doses in oily suspensions frequently caused exacerbations of the rheumatic process. This can probably be explained by the stimulation of the adrenals by desoxycorticosterone as suggested by Lewin and Wassén or by the reactive excretion of cortisone by the adrenals induced by the hypoglycemia. Both mechanisms probably play a part. The clinical result is satisfactory with prolonged administration of small doses, which avoids counter regulation. This is shown by the mobility of the joints, the basal metabolism, body temperature, and decrease of the eosinophils. The authors suggest that this treatment be limited to cases in which the salicylates have failed and to those in which signs of endocarditis or myocarditis are beginning to appear, because, in case of faulty application, the secondary effects are likely to be serious.

Chemotherapy in Skeletal Tuberculosis. I. G. MacKenzie. Lancet **1**:652-654 (March 27) 1954.

MacKenzie, in treating skeletal tuberculosis, uses a radical method of local treatment abandoned 50 years ago because it was too often followed by sinus formation and dissemination of the disease. With this method and the use of chemotherapy, the complications secondary to general treatment of the disease have decreased, the period of rigid immobilization has been shortened, and it is hoped that its untoward effects in favoring the formation of renal calculi, osteoporosis, and premature epiphyseal fusion with the high foot will also decrease. General treatment of the disease is still essential to heal the lymph node focus of the infection. The diagnostic methods have also been changed since the advent of chemotherapy. The former theory of "wait and see" has become "look and see." Early diagnosis and early proof of the nature of the lesion while still in the synovial stage is now imperative, and among the methods used is synovial biopsy. The surgical technique of local treatment has also been modified. The diseased joint is opened, the sequestra and tuberculous granulation tissue are scraped out, and the resulting cavity is packed with bone chips to obtain solid bone fusion across the site of the disease even in the spine. Despite all these modifications, the principles of local treatment of skeletal tuberculosis remain the same. 1. A tuberculous lesion requires local rest to prevent deformity and to favor local healing. 2. Extra-articular foci should be excised, when possible, before the adjacent joint becomes involved. 3. Tuberculous pus should be removed as soon as it is formed. 4. Every effort should be made to heal sinuses and prevent secondary infection. 5. The ultimate aim is to obtain either a freely mobile joint or a sound bony ankylosis. Chemotherapy should not be used indiscriminately but should be reserved for critical phases in the course of the disease such as progressive lesions, multiple lesions, sinuses, operations, and synovial infections. The antibiotics will shorten the course of skeletal tuberculosis.

Paradoxical Hyperglycemia in Diabetic Patients Treated with Insulin. G. T. Perkoff and F. H. Tyler. Metabolism **3**:110-117 (March) 1954.

Perkoff and Tyler made studies on 10 patients with so-called paradoxical hyperglycemia. The clinical characteristics of this phenomenon are (*a*) deterioration of diabetic regulation on increasing insulin doses, (*b*) infrequent clinical hypoglycemic reactions, (*c*) cyclic glycosuria, and (*d*) improved diabetic regulation on reduced insulin dosage. The elderly diabetic patient manifesting this phenomenon can be treated by greatly reducing the insulin dosage. Juvenile diabetics, on the other hand, require gradual reduction of the insulin dose by very small amounts. The determination of hourly glucose excretion may prove to be a simple clinical test for the recognition of parodoxical hyperglycemia. The phenomenon of paradoxical hyperglycemia can become manifest in patients receiving regular insulin as well as in those receiving long-acting preparations. However, in individual patients the type of insulin may be important in that one form may cause hypoglycemia at a specific time of day, whereas similar amounts of another kind may not.

Smoking and Lung Cancer. W. L. Watson and A. J. Conte. Cancer **7**:245-249 (March) 1954.

From 1950 to 1952, a total of 769 consecutive patients were studied at the Thoracic Clinic of the Memorial Hospital in New York City. Of this group, 301 had histologically and/or cytologically proved cancer of the lung—265 men and 36 women. The other 468 patients—287 men and 181 women—with problems related to the chest served as control for this study. All were divided into three groups on the basis of the patients' smoking habits. Patients who smoked less than 20 cigarettes a day were classified minimal smokers, those who smoked up to 20 cigarettes a day for 20 or more years moderate smokers, and those who smoked 20 to 60 cigarettes a day for 20 or more years heavy smokers. One pipe was considered equal to two and one-half cigarettes and one cigar to five cigarettes. Of the 265 men with cancer of the lung, 73% were heavy smokers, as compared to 57% of the 287 men who did not have cancer of the lung; 24% were moderate smokers; and 3% were minimal smokers. Of the 287 control men, 9.7% were nonsmokers, as compared to 1.8% of those with cancer of the lung. These statistically significant differences give strong support to the argument that smoking must play a significant role in the background of patients in whom cancer of the lung develops. Neither racial nor national background seemed to have any influence. Of the 36 women with proved cancer of the lung, 58% were nonsmokers as compared to 82% of the 181 control women, and the number of women with cancer who smoked was slightly more than twice that of the control women who smoked. All of the smokers were classified as either minimal or moderate smokers. Although the number of women studied is relatively small, smoking must be of significance. It is noteworthy that the number of women with carcinoma of the lung admitted to this clinic in the last 20 years has been increasing very slowly in comparison with the marked increase in the incidence of this disease in the men admitted. The ratio in this study was more than seven men to one woman. The results of this study add to the growing evidence that the incidence of cancer of the lung is increasing, and they seem to support the hypothesis that smoking, when quantity and chronicity are considered, probably represents an additional carcinogenic factor in the onset of squamous and epidermoid lung carcinoma.

Hormonal Therapy in Cancer of Breast: VI. Effect of ACTH and Cortisone on Clinical Course and Hormonal Excretion. A. Segaloff, R. Carabasi, B. N. Horwitt and others. Cancer **7**:331-334 (March) 1954.

The effects of corticotropin (ACTH) and cortisone on carcinoma of the breast were studied in 19 women whose ages ranged from 23 to 85 years. Ten patients had soft tissue lesions only, five had skeletal lesions only, and four had both soft tissue and skeletal lesions. All the patients had undergone ovariectomy or the menopause from 1 to 45 years before this therapy was instituted. Seven were given corticotropin by eight hour continuous intramuscular injection for an average of 6 weeks; the other 12 received cortisone intramuscularly once daily as a saline suspension containing 25 mg. of cortisone acetate per cubic centimeter plus suspending agents. Three of these received 10, 25, and 50 mg., respectively, while nine were given 100 mg. daily for an average of 11 weeks. The therapy was considered a failure if one or more lesions increased in size even though others decreased. Objective regression of lesions was considered to be

present when all lesions decreased in size or most of them became small, while the others remained stationary. There was no evidence of objective regression of lesions in any patient; in two in whom extensive pulmonary lesions did regress, lesions progressed elsewhere. The subjective improvement was, however, often most gratifying, despite the obvious progression of the disease. This was especially true of some patients who had pulmonary lesions and severe dyspnea. In these patients the continuous administration of oxygen required before therapy was no longer necessary. In the other patients the subjective improvement was evidenced by reduction in narcotic requirements and increase in appetite and well-being. Creatinuria increased and was accompanied by a decrease in urinary creatinine. According to the authors, this feature is associated with progression of the disease except during the administration of the 17-methylated steroids. Although it is generally believed that the effects of cortisone and corticotropin are similar and, therefore, both hormones can be used interchangeably in most instances, cortisone tended to increase the excretion of both gonadotrophins (as measured by the mouse uterine weight method) and prolactin, while, in direct contrast to this, corticotropin actually decreased the excretion of both. As expected, the patients given corticotropin showed a greater increase in the urinary excretion of the 17-ketosteroids and formaldehydogenic corticoids than did those who received cortisone. There were no essential changes in pregnanediol, and the excretion of uric acid increased about the same for both groups of patients. Seven patients for whom data were available showed lower gonad-stimulating hormone values than would be expected for their age and endocrine status.

Use of ACTH and Cortisone in Leukemia and Lymphoma. W. H. Griffith and C. F. Gutch. J. Iowa M. Soc. **44:**117-122 (March) 1954.

Corticotropin (ACTH) and cortisone were given to nine men with leukemia and lymphoma at the Veterans Administration Hospital, Lincoln, Nebr. One patient with acute granulocytic leukemia was given corticotropin. He experienced a transient reduction of fever and of general toxicity during the first 72 hours. Symptoms then became worse, and he died on the fifth day of treatment. One patient with monocytic leukemia in a terminal stage was given cortisone for five days. There was also a transient reduction in fever and toxicity for 48 hours followed by an exacerbation of symptoms. Death occurred on the seventh day. Three patients with acute lymphocytic leukemia were treated with cortisone, corticotropin, 4-aminopteroylglutamic acid, transfusions, and nitrogen mustard in various combinations. Periods of clinical improvement varied from 4 to 10 weeks. Reduction in the size of lymph nodes, spleen, and liver took place in the three patients. There was a reduction in total white blood cell counts and improvement in hemoglobin values for variable periods in the three patients. The need for transfusion was diminished. The three patients died in a fulminating exacerbation while receiving cortisone or corticotropin. One patient with leukemia cutis complicating chronic lymphatic leukemia was unable to tolerate 80 mg. of corticotropin per day and cardiac failure developed. There was no significant improvement in his skin lesions. One patient with mycosis fungoides, apparently caused by reticulum cell sarcoma, received corticotropin in doses up to 160 mg. per day. The skin lesions improved, but did not disappear. Anemia did not improve. Pronounced salt and water retention developed even with reduced doses of corticotropin. Intense melanin deposits in the skin appeared while the patient was receiving the hormone. He had a subsequent excellent response to nitrogen mustard therapy. On two occasions, a 60-year-old patient with multiple myeloma was completely relieved of incapacitating abdominal discomfort and nausea by corticotropin. His need for transfusions was reduced, there was reduction in his serum globulin level from 8.29 gm. per 100 cc. to 5.3 gm. per 100 cc., and his albumin level increased from 1.9 to 3.01 gm. per 100 cc. Death resulted from renal failure 12 days after the second course of corticotropin was completed. One patient with Hodgkin's disease was given corticotropin in doses of 75 mg. per day. Fever and toxicity were significantly improved. There was no change in peripheral or mediastinal lymph nodes. Exacerbation of fever occurred after the use of corticotropin was discontinued, despite roentgen irradiation therapy. There was no response to cortisone, and he had a hemolytic episode while treated with this drug. There was no response to a further course of nitrogen mustard, and the patient died. Cortisone and corticotropin are not substitutes for other forms of therapy such as transfusions, x-ray, nitrogen mustard compounds, urethane, and folic acid antagonists. The indications for these agents have not changed. In some cases, the steroid compounds may be combined with other therapy to prolong or induce a remission that might not otherwise occur. They enable some patients to be active to a degree that would otherwise be impossible, but the unfavorable prognosis is not altered. Patients with a proliferative leukocytic disease have extensive neoplastic infiltrates, and myocardial or renal insufficiency may be precipitated abruptly by corticotropin or cortisone in amounts not adequate to control the symptoms of the disease.

Lead Poisoning Following the Use of an Oxy-Acetylene Torch: Report of Four Cases. A. Bell. New Zealand M. J. **53:**57-60 (Feb.) 1954.

A large gold dredge was being dismantled by cutting off the heads of rivets with oxyacetylene torches. Men who had been working on the upper horizontal decking of the pontoon of the dredge for about three weeks all complained of excessive thirst and slight headaches. Bell was told that the pontoon had been painted with red lead paint when it was assembled approximately 12 years ago, and analyses of paint scrapings taken from its hull determined the lead concentration at 40%. When he watched one of the men at work, it was obvious that, in spite of possible wind, the worker would breathe large quantities of fumes created by the burning paint, as the rising hot fumes were not substantially dispersed until they were well past his breathing zone. Tests revealed that the men were inhaling approximately 120 times more than the suggested maximum of allowable concentration of atmospheric lead. The four men who had used the oxyacetylene torch to remove rivets from the lead-painted pontoon were studied for stippled cell count, hemoglobin content, presence of pallor, and blue line around the gums, and they were asked about symptoms, appetite, metallic taste, dyspnea, abdominal pain, and constipation. Because of the extremely heavy concentration of atmospheric lead at the men's breathing zone, the author did not believe that the conventional type of filter pad respirator, covering nose and mouth, would afford adequate protection. The question of the men's using a respirator with its own independent airline was ruled out, as it would have been awkward. In view of these difficulties and of the fact that practically all industrial lead poisoning is due to the inhalation of dust and fumes, it was suggested that the rivets should be removed either with a pneumatic rivet gun or with hammer and chisel. It is commonly assumed that if a potentially toxic process is carried out in the open air it is almost invariably safe because of general ventilation. In many cases this is correct, but this report illustrates that this is not necessarily the case.

Diffuse Scleroderma. H. Zettel. Chirurg. **25:**121-126 (March) 1954. (In German.)

Diffuse scleroderma is reported in three women and one man between the ages of 40 and 55. The man had severe diffuse scleroderma with particular involvement of the face, neck, breast, hands, and feet. There were severe disturbances in circulation of the type seen in Raynaud's disease, particularly in the hands, with a large ulcer on the right thumb. These disturbances improved considerably after the administration of hydergine (a mixture of the three hydrogenated alkaloids dihydroergocormine, dihydroergocristine, and dihydroergokryptine); pain subsided, the ulcer healed within a few weeks, and new ulcers did not occur. Dyspnea, however, increased and the work capacity diminished. There was intolerance of food containing large amounts of fat, and vomiting occurred after large meals. Severe sclerosis of the esophagus, atrophy of the mucous membrane of the stomach with only little superficial peristalsis, and considerable dilatation of the upper jejunum were revealed by roentgenologic examination. The lungs showed honey comb structure in both lower lobes. Results of bronchoscopy and repeated roentgenograms suggested pulmonary fibrosis (multiple cyst formation with fibrous shrinking). History did not furnish

any evidence of the cause of the disease. The study of cases of severe diffuse scleroderma shows the polymorphism of the disease. The skin is only one of the many organs to be involved. Further intensive research is required for clarifying the pathogenesis of scleroderma. It seems advisable to consider more than was done hitherto the changes in the sympathetic nervous system, disturbances of the hypophysis and the diencephalon, and disturbances of the protein metabolism. Scleroderma is not essentially a cutaneous disease and, therefore, should not be the exclusive domain of the dermatologist. The polymorphism of the disease justifies the assumption that internal medicine and surgery should be able to contribute to the much needed clarification.

SURGERY

A Case of Spontaneous Regression of an Untreated Bronchiogenic Carcinoma. B. Blades and R. G. McCorkle Jr. J. Thoracic Surg. **27:**415-419 (April) 1954.

A 59-year-old man who had suffered from chronic bronchitis for 20 years gave a history of malaise and increasing dyspnea of two months' duration and an 18 lb. (8 kg.) loss of weight over a period of six months. Roentgenograms of the chest revealed an opacity in the right lung field at the level of the third and fourth intercostal spaces anteriorly. Thoracotomy was performed that revealed a carcinoma of the lung with involvement of the right hilum and invasion of the mediastinum at the level of the inferior pulmonary artery. A biopsy of the mass was taken, and, since the lesion appeared inoperable, the chest was closed. Microscopic examination of the tissue revealed an epidermoid carcinoma. Roentgenograms of the chest revealed progressive clearing of the pulmonary lesion in the right lung six months after the exploratory thoracotomy. No physical abnormalities could be detected on physical examination five years after the lung cancer had been detected. Significant changes were observed on the roentgenograms of the chest. There was a 3 cm., irregular density in the left second interspace anteriorly, that had not been present on previous chest films. The almost complete disappearance of the original lesion in the right lung was constant, corresponding to roentgenograms of the past four years. In the lateral view of the skull, a destructive lesion could be demonstrated in the occipital bones. No explanation was found for the regression of the lung cancer. The postoperative temperature elevations were not high and cannot be regarded as significant. Drugs used by the patient were not considered important and did not have carcinolytic properties. This case represents the only known instance of spontaneous regression of a bronchogenic carcinoma. Despite evidence of metastasis to the skull, the patient remained in good health more than five years after the original diagnosis of bronchogenic carcinoma.

The Fate of Patients with Alveolar-Cell Tumor of the Lungs. T. W. Mears, J. W. Kirklin and L. B. Woolner. J. Thoracic Surg. **27:**420-424 (April) 1954.

Ten women and three men between the ages of 30 and 66 years with alveolar cell tumor of the lungs were treated by surgical excision at the Mayo Clinic. Three patients did not have symptoms referable to the thorax when first examined. The average duration of symptoms in the remaining 10 patients was 11½ months. The commonest symptoms were cough, dyspnea, fever, pain in the thorax, and hemoptysis. The lesions were demonstrated on roentgenologic examination of the thorax, but their appearance was not diagnostic. The usual significant finding at bronchoscopy was a frothy mucoid sputum coming from the involved segments of the lung. Either the bronchial washings, the sputum or both were positive for malignant cells in 7 of the 11 patients in whom preoperative cytological examination was done. Lobectomy was the operation of choice in 10 patients, and pneumonectomy was carried out in the remaining 3. The left lower lobe was resected in eight patients and the left upper lobe in two. The right upper lobe was removed in two patients, and all three pneumonectomies were on the right side. Roentgen irradiation was used in addition to surgical excision of the lesion in four patients, but the course of the disease evidently was not altered in any of the patients. Two patients died in the immediate postoperative period and necropsy did not show evidence of residual tumor. Two patients who survived the operation died of other causes. Five patients who died showed evidence of recurrent disease. Only 4 of the 13 patients are living, and 2 of these have evidence of recurrent tumors. Of the two who do not show evidence of recurrence, one has survived the operation for four years and the other one year. Although the results of treatment are disappointing, the only method of treatment of even palliative value at the present time is conservative surgical excision of the affected portions of the lung.

Congenital Cystic Lung: Successful Pneumonectomy in a Three-Week-Old Baby. G. G. Crowe. J. Thoracic Surg. **27:**399-401 (April) 1954.

Congenital cystic lung in a 10-day-old baby gave rise to great respiratory distress that did not respond to simple measures like the needling of the cyst cavity. Thoracotomy was carried out through the bed of the fifth left rib when the dyspneic and cyanotic child was 23 days old. On opening the pleura, the upper lobe was found to contain a large cyst that was filled with air and appeared to have a large communication with the bronchus. The lower lobe also contained several fairly large cysts. Left total pneumonectomy was performed. In the course of the operation and during the postoperative period, the child was given 450 cc. of Hartmann's solution and about 50 cc. of blood. After the operation, the patient received 70 mg. of streptomycin twice a day and a course of chloramphenicol (Chloromycetin). She made a satisfactory recovery, but the convalescence was complicated by discharge from the wound that persisted for about six months before it finally healed. Eleven months after the operation, the child's condition was very good. The remarkable ease described by other workers with which lobectomy and pneumonectomy can be done in infants was noted again in this patient. Dissection of the structures in the hilum is remarkably simple and can be rapidly carried out.

Bicipital Tenosynovitis. P. R. Yedinak and B. G. Holbrook. Rocky Mountain M. J. **51:**185-191 (March) 1954.

Painful shoulder and the "frozen shoulder syndrome" occur frequently and result in serious disability. In the early stage, the patient complains of pain at the extremes of abduction and rotation. The pain is referred chiefly to the anterior region of the shoulder, anterior surface of the arm, or even to the flexor surface of the forearm. The patient seen later in the course of this disease not only complains about pain in the shoulder, but of stiffness and limitation of motion as well. The range of shoulder motion at the scapulohumeral joint may progressively diminish. The pain becomes constant and interferes with rest and sleep, and occasionally it may spread from the shoulder into the neck. With lack of use, the shoulder girdle muscles become atrophic and the prominence of the shoulder is flattened. The pathological clarification of the syndrome involved years of work by several investigators. Invariably there is evidence of inflammation of the tendon of the long head of the biceps brachii muscle and its sheath. The tendon may be bound to the sheath with multiple fine fibrous adhesions and the sheath injected and somewhat edematous. In more advanced disease, the tendon is frayed, there is partial disruption, and the tendon sheath is thickened and fibrous. Granulations may be demonstrable throughout the bicipital groove. In prolonged cases, the tendon is bound to the floor of the groove by tough adhesive bands. The intertubercular groove may have a bony roughening or excrescence. The local peculiarity of the anatomy gives further clarification of the problem of the long head tendon. The two large gliding surfaces produced respectively by the deltoid cowl and the deeper hood formed by the musculotendinous cuff provide opportunity for adhesion and agglutination between gliding surfaces. With the shoulder forced to relative or complete immobility by pain, venous and lymphatic stasis occur, the local metabolism is altered, and the gliding surfaces become covered with serofibrinous exudate and are later glued by the organization of the exudate to fibrous adhesions. In the initial phases of the disease, when inflammatory changes have not become irreversible, con-

servative treatment with sedation for pain, application of heat, local procaine injections, and exercises may be successful. If such measures fail, surgical treatment may be necessary. In four of the five illustrating case histories, the tendon of the long head of the biceps was transferred to the coracoid process with satisfactory results.

Sympathectomy by Axillary Approach. H. J. B. Atkins. Lancet **1**:538-539 (March 13) 1954.

Atkins removed the upper part of the sympathetic chain through the axilla in 42 operations on 26 patients. Raynaud's disease, thromboangiitis obliterans, causalgia, hyperhidrosis, and cardiac pain were the conditions for which sympathectomy was undertaken. In this report he is not concerned with the relief obtained, but confines himself to a description of the procedure, which was devised by Schulze and Goetz of Cape Town, and its complications, advantages, and disadvantages. The results on the whole were no better or worse than those of sympathectomy performed by other routes. With the axillary approach, it is possible to see the upper part of the thoracic sympathetic chain shining through the parietal pleura. The adjacent intercostal veins, which in other approaches may cause trouble, can be readily identified and avoided. The stellate ganglion and the second thoracic and third thoracic ganglions should be identified before the parietal pleura over them is disturbed; otherwise the slight oozing, which occurs as soon as the pleura is incised, tends to mask the anatomy of these parts. Having used the anterior, posterior, and axillary approaches to the upper part of the sympathetic chain to an almost equal extent, the author is able to compare the axillary with the other two approaches. If the purpose of the operation is to expose the thoracic sympathetic chain below the third ganglion, without interfering with the stellate ganglion itself, the axillary approach is incomparably the easiest. Thus, the second and third thoracic ganglions are preferably removed via the axilla. Removal of the fourth or fifth ganglion, which may be necessary when operating for cardiac pain, cannot be done conveniently except by this approach. The stellate ganglion may be a little awkward to reach through the axilla. If only the stellate ganglion is to be removed, the anterior approach is the best. The axillary approach compares favorably with the posterior approach in regard to accuracy and is more reliable in this respect than the anterior approach. The author has less difficulty with controlling hemorrhage when using the axillary than the other two approaches. Trauma to tissues is about the same in the axillary and anterior routes; the posterior approach, however, is much more traumatic. The incision in the axilla heals well and is unnoticeable. In this respect the axillary approach has a slight advantage over the anterior, and a great advantage over the posterior approach. Disadvantages of the axillary approach are that the operation cannot be performed on both sides at the same session. If, in case of vascular abnormality of the hands and fingers, there is doubt about the diagnosis as between peripheral vascular disease and the costoclavicular syndrome, one cannot investigate the latter possibility at the time of the operation as can be done with the anterior approach. A history of phthisis contraindicates the axillary approach. The author recommends the axillary approach in suitable cases.

Hip Fractures in General Surgery. B. B. Baughman. Am. Surgeon **20**:317-331 (March) 1954.

This paper is based on the observations of a general surgeon in the treatment of 80 patients with fractures of the upper end of the femur. These patients were treated by internal fixation over a period of 15 years. Forty-eight fractures were of the neck and 32 were of the trochanteric region. Five patients died either as the result of the fracture or the operation during the first 17 days; four of these had fractures of the femoral neck. There were no deaths in the last 27 patients operated on. Bony union was obtained in all of the neck fractures, but two of the trochanteric fractures resulted in nonunion. Avascular necrosis was observed in one of the neck fractures. Except in acutely ill or moribund patients, all fractures, including the impacted ones, should be nailed. The best way to obtain uncomplicated union is by accurate reduction and firm, prolonged internal fixation, without weight bearing until union is seen in the roentgenogram. Difficulties found in trochanteric fractures were coxa vara deformity, shortening, arthritis, limp, and overdrive causing protrusion of the nail into the hip joint. The best material for internal fixation is the stainless steel cannulated Smith-Petersen nail for neck fractures and the nail and Thornton or McLaughlin plate, or the Jewett appliance for trochanteric fractures. All fractures should be operated on within 24 to 48 hours. Neck fractures may be satisfactorily operated on without traction and on a roentgen ray table. Displaced trochanteric fractures should be operated on in traction on a fracture table. The nailing of the subcapital, vertical fracture should be supplemented by bone grafting. Anteroposterior and lateral roentgenograms are indispensable. Good general anesthesia and adequate blood transfusions during operation insure a low mortality rate.

Result of Vagotomy in Treatment of Anastomotic Ulcer. B. W. Wells. Lancet **1**:598-599 (March 20) 1954.

Thirty-nine cases of proved anastomotic ulceration treated by vagotomy were followed up. Twenty-five patients had undergone partial gastrectomy, and the rest gastroenterostomy. The results in the first group show that vagotomy is not a completely satisfactory method of treatment, since it gave only two-thirds of the patients freedom from recurrence in a follow-up of about three years. Nevertheless vagotomy may be worthy of trial in such cases because it is safer than the alternative of a more radical gastrectomy. The results were worse in the patients who had gastroenterostomies; 10 out of 14 had definite or suspected recurrence. The author concludes that vagotomy alone has no place in the treatment of such cases.

Treatment of Chronic Osteomyelitis with Flaps. E. A. Kitlowski. Am. J. Surg. **87**:351-356 (March) 1954.

According to Kitlowski, chronic osteomyelitis frequently fails to heal because of the fibrosis in the soft parts that reduces the blood supply. The circulation can be improved by excision and relaxation of the indurated and fibrosed areas and by covering the defects with normal tissue. The most desirable coverage is with skin and fat in the form of flaps. The flaps can be secured from the sides of the same leg if the tissue is fairly normal and the defects created by the shifting flaps can be covered with split grafts. The flap can be secured from the opposite leg or the abdomen, if the tissue on the affected leg is not satisfactory for a shift. In case it is not possible to cover the area with a flap, skin grafts either in the form of splint grafts or small deep grafts can be used to cover the defect created by excision of the indurated tissue around the involved bone.

Rectal Sphincter Reconstruction Using Gracilis Muscle Transplant. K. Pickrell, F. Masters, M. Georgiade and C. Horton. Plast. & Reconstruct. Surg. **13**:46-55 (Jan.) 1954.

Pickrell and associates subjected 12 children to rectal sphincter reconstruction by utilizing the gracilis muscle. Continence of feces and gas was achieved in each instance. Eleven of the 12 children who have had the gracilis sling operation were incontinent from birth because of spina bifida, meningocele, or some congenital neurogenic malformation involving the perineum and rectum. The remaining 3-year-old child had the perineum and anus chewed away when attacked by a sow. This was the youngest child that has been operated on. The ages of the other children ranged from 4 to 12 years. The patients were boys except in one instance. The authors believe that the optimum age for the transplant operation is between 4 and 5 years. This will spare the child the psychological insult of incontinence at school. It should be emphasized that voluntary, controlled continence develops in these patients. However, it is not so automatic as the normal sphincter mechanism. These patients were social outcasts, and, as such, they were extremely anxious to learn to use the new sphincter mechanism, and continence developed in each instance. Several patients have been followed for more than five years.

NEUROLOGY & PSYCHIATRY

Oral Cortisone Treatment of Hypopituitarism. H. L. Sheehan and V. K. Summers. Brit. M. J. **1**:723-726 (March 27) 1954.

The authors' series of patients comprises three women with typical severe postpartum hypopituitarism and one man with hypopituitarism presumably caused by atrophy. They were all successfully treated with small doses of cortisone given orally over a period of about two years. Discontinuance of the drug for three months after the first nine months of treatment in three patients produced a return of symptoms. It is interesting that cortisone influences characteristically hypothyroid symptoms of hypopituitarism such as mental slowness and lack of interest, physical sloth, extreme sensitivity to cold, and absence of sweating whereas thyroid does not. Testosterone is effective in restoring physical and mental activity in hypopituitarism, but not to so great an extent as cortisone; on the other hand, testosterone promotes growth of body hair, which cortisone does not. Combined therapy was tried by the authors, but no definite additive effect was observed beyond that on body hair. If, after combined therapy, the administration of testosterone is stopped, the patient's condition will remain as good as before, but if the administration of cortisone is stopped, the patient's condition will deteriorate while receiving testosterone alone. Detailed studies are required to determine the effect of each of the various substances that are commonly prescribed for the treatment of hypopituitarism (thyroid, estrogens, desoxycortisone, sodium chloride, and various vitamins) in patients who are being given maintenance treatment with cortisone. The only observation the authors have made of this sort is that in some cases puffiness of the eyes is reduced by a combination of thyroid and cortisone, but by neither separately. The authors think that cortisone therapy is the most useful method of long-term treatment of patients with hypopituitarism. A dosage of 12.5 mg. orally a day appears to be adequate for maintenance. A dosage of 25 mg. is equally satisfactory, but it does not produce a proportionate improvement in the signs or symptoms. Larger doses, such as 50 to 100 mg. a day, are very apt to produce transient mental disturbances; this is in marked contrast to the tolerance of large doses shown by patients with rheumatoid arthritis.

The Attitude of the Patient Toward Multiple Sclerosis. M. Tarlau. New York J. Med. **54**:680-682 (March 1) 1954.

In an effort to obtain opinions of patients with multiple sclerosis on the value of having this diagnosis disclosed to them, the National Multiple Sclerosis Society, in the October, 1951, issue of its bulletin, published a questionnaire and requested that its readers answer the following three questions. 1. Do you think that patients with multiple sclerosis should be told of their diagnosis? Why? 2. What is your opinion regarding the advisability of multiple sclerosis patients attending meetings? 3. Why did you join the National Multiple Sclerosis Society? In reply to the first question 290 of 327 patients with such a diagnosis replied in the affirmative, while nine were opposed and 27 gave a qualified answer. The reasons given for their answers were (1) better adjustment would follow disclosure and (2) not knowing the basis for the symptoms had adverse effects, such as vague worry or fear of neurosis. Stress was put on the need for tact in disclosing the diagnosis to the patient and on the need of preparing the patient for the disclosure. The majority of respondents were in favor of attending meetings. Of the total number, 237 were members of the National Multiple Sclerosis Society because of the helpful information that might be received either from research results or from publications of the society. Since a very great majority of patients favor the disclosure of the diagnosis of multiple sclerosis to the patient, the author feels that as a general rule the physician should inform the patient of his disease.

Contribution to Morgagni's Syndrome. E. Ketz. Ärztl. Wchnschr. **9**:277-281 (March 19) 1954. (In German.)

Among patients who were referred to the neurological section of the hospital of the University of Berlin because of severe headaches resisting all therapeutic efforts, Ketz found eight patients who presented the characteristics of Morgagni's syndrome. The headaches are usually of a migraine type and for this reason frequently cause diagnostic and therapeutic difficulties. The other outstanding symptoms are the triad of internal frontal hyperostosis, virilism, and obesity. There may also be hypertension, diabetes mellitus, and mental disturbance. Cerebral convulsions occurred in one of the cases. The psychological disturbances resemble those of the so-called diencephalic syndrome. Pathogenetically, the disease is probably a central regulatory disturbance in the diencephalohypophysial system, which in turn may be the result of hereditary predisposition or disturbances in the hormonal equilibrium. Treatment is largely symptomatic to combat the severe headache and hypertension. The authors resorted chiefly to the use of the sympathicolytic drug, Hydergine, that is a mixture of methanesulfonates of dihydrogenated ergotoxine alkaloids. The action of hydergine is probably due to the ergot alkaloids that have not only a sympathicolytic effect but also a sedative effect in that they reduce the vascular tonus. The authors also employed blockage of the sympathetic (stellate ganglion) by means of procaine hydrochloride injection. Substitutional hormone therapy completely failed in Morgagni's syndrome.

Pathologic Anatomy of Ruptured Cerebral Aneurysms. G. Wilson, H. E. Riggs and C. Rupp. J. Neurosurg. **11**:128-134 (March) 1954.

Wilson and associates report anatomic observations in 143 autopsied cases of subarachnoid hemorrhage caused by leaking miliary or berry aneurysms of the circle of Willis. Women predominated 91 to 52, and about one-third of the patients were less than 40 years old. The aneurysms were located above the carotid siphon on the circle of Willis, its peripheral branches or its basivertebral component. The aneurysmal sac originated at arterial branchings, although not necessarily at a bifurcation, in 101 cases, and by outpouchings from the vascular stem in 42. Multiple aneurysms were present in 27 patients. Evidence of repeated bleeding, either ancient or recent, was present in most cases. Parenchymatous lesions were present in 94 cases, but hemorrhage accounted for only 29. Little attention has been paid to the factors that precipitate bleeding from cerebral aneurysms. The authors regard it as significant that hypertrophy of the heart, particularly of the left ventricle, was present in 27 of the 40 patients under 40 years of age. Dissecting aneurysm of the aorta, severe coronary sclerosis, or fibrosis of the myocardium were present in three patients, the oldest of whom was 30. Rheumatic valvular disease was noted in three, pericardial effusion in two, and adhesive pericarditis in one—all under 40 years of age. In this younger group, subarachnoid bleeding occurred during active pulmonary tuberculosis in one patient and during a crisis of sicklemia in another. Of the 97 patients over 40 years of age, 41 were under treatment for cardiac disorders prior to the onset of the subarachnoid bleeding; 15 additional instances of syphilitic or rheumatic heart disease were found post mortem. Patent foramen ovale was noted in three cases, pericardial effusion in one, and a large aneurysm of the aortic arch in another. Subarachnoid bleeding occurred in three chronic alcoholics during a debauch and in one patient at the onset of diabetic acidosis. Anomalous formation of the circle of Willis was present in 118 of the 124 cases with cerebral aneurysm in which complete description was available. The anomalies of the circle of Willis were of a type that would interfere with adequate collateral circulation. These factors have to be considered in evaluating the potentialities of surgical therapy.

Intracranial Aneurysms: II. Some Clinical Observations Concerning Their Development in Posterior Circle of Willis. R. C. Bassett and L. J. Lemmen. J. Neurosurg. **11**:135-142 (March) 1954.

Most aneurysms of the cerebral circulation represent vestiges of the primitive circulatory system in the embryo. Bassett and Lemmen had demonstrated this on the basis of a series of cases with reference to the anterior circle of Willis in a paper published in 1949. They report six cases in which there were aneurysmal residuals and abnormal vascular patterns of the posterior circle of Willis. The case histories and necropsy reports of these patients are followed by a discussion of the em-

bryologic factors concerned in the development of the cerebral vascular tree, which provide an acceptable explanation of the pathological anatomy of these intracranial aneurysms.

Carpal Tunnel Syndrome in Acromegaly. F. Schiller and F. O. Kolb. Neurology **4**:271-282 (April) 1954.

Schiller and Kolb present histories of four patients with the carpal tunnel syndrome (partial thenar atrophy). Three of these patients had acromegaly and one had myxedema. The first patient was a man, aged 38, who, 10 years before, had first noted progressive enlargement of face, hands, and feet. Two years after his hands began to enlarge (eight years before hospital admission), he was disturbed by tingling and pain occurring simultaneously in the thumb, index, and middle fingers of both hands. The pain and tingling of his hands grew less over a period of many months, but at the same time the ability to feel the texture, shape, and temperature of objects was gradually lost in the affected fingers. There was an almost horizontal groove at the base of each thenar eminence, resulting from the wasting of the abductor pollicis brevis. In this patient, there was some recovery of sensation in the region of the median nerve after a sizable eosinophilic adenoma had been removed from the pituitary. The second patient, a woman aged 41, had acromegaly with bilateral partial thenar atrophy; there was slight paresthesia, but no sensory loss. There was some improvement in headaches after roentgen irradiation of the pituitary, but six months later no subjective or objective change in the appearance of the hands was noticeable. In the third patient, a man of 56, asymptomatic bilateral partial thenar atrophy was discovered 35 years after onset of acromegaly; there was no sensory loss. The fourth patient, a 59-year-old woman, complained of an annoying tingling sensation in the thumb and index finger of her right hand. The sensation had been present for the past year and had started six months after initiation of treatment for advanced myxedema. In trying to find a common denominator for the spontaneously occurring carpal tunnel syndrome and that seen in patients with acromegaly and rarely myxedema, it seemed significant that the carpal tunnel syndrome occurs principally in patients with certain endocrine disorders, that is, in women past the menopause and patients with acromegaly. These two endocrine disorders have several features in common, including a coarsening of features. Assuming that estrogens suppress the pituitary, does the hypogonadal state of the menopause conversely bring out the proliferative effects of pituitary growth hormone? The effects of such stimulation on connective tissue growth would be most likely to appear in a tight compartment such as the carpal tunnel. In that case, treatment with estrogens in the early stages of the disease seems logical. Three patients with menopausal median neuropathy were observed by the authors in whom this treatment caused the digital pain to disappear.

Effects of Prolonged Alcoholic Excess. J. Isbister. M. J. Australia **1**:360-363 (March 6) 1954.

Isbister defines chronic alcoholism as a state of physical or mental invalidism produced by prolonged, excessive intake of ethyl alcohol in its various forms. He disregards the mental and social aspects of chronic alcoholism and presents the results of an analysis of 86 patients who were hospitalized because they were physically ill. These patients were not admitted for the treatment of chronic alcoholism as such. The group is entirely unselected, most of those admitted having been referred by general practitioners to a general hospital. The information was compiled from routine ward clinical notes. Emphasis was placed on the final diagnosis. The group included 56 men and 30 women. The average age of the men was 47 and that of the women 52. A large proportion of the men were bachelors; widows accounted for a somewhat smaller proportion of the women. Cirrhosis of the liver is the commonest disease caused by chronic alcoholism, women being especially liable to cirrhosis without portal hypertension and men contributing the majority with portal hypertension. Beriberi heart disease is a relatively common condition and is confined almost entirely to men. It also appears to have a periodic incidence. Peripheral neuritis, Korsakoff's syndrome, and Wernicke's encephalopathy are conditions that predominate in women. Lung abscess should be considered in all cases of pneumonia occurring in alcoholics. The causes of these differences with regard to sex, marital status, and the disease syndrome produced are not clear. Undoubtedly constitutional differences in the two sexes are partly involved. The clue is probably in the dietary intake. If really reliable dietary histories could be obtained in all cases, there might be some correlation between the type of dietary deficiency, sex, marital status, and disease syndrome produced.

Alcoholic Polyneuritis: Its Treatment with Vitamin B_{12}. G. Murphy. Prensa méd. argent. **41**:804-806 (March 19) 1954. (In Spanish.)

Murphy comments on the cause of alcoholic polyneuritis and on the fact that there are some cases that fail to respond to large doses of thiamine, vitamin B complex, and liver extracts. The fact that vitamin B_{12} proved highly effective in funicular myelitis of pernicious anemia indicated its neurotropic effect and suggested its possible use in polyneuritis. Favorable results obtained with vitamin B_{12} in various forms of polyneuritis induced Murphy to use it in nine patients with alcoholic polyneuritis who were selected from among 17, because of the severity of symptoms and because they had not yet been treated with vitamins and liver extracts likely to obscure the results obtainable with vitamin B_{12}. All nine were men and heavy drinkers. Four of them had delirium tremens, one was in a confusional state associated with polyneuritis, and the other four had polyneuritic disturbances. In addition to their neuropsychiatric symptoms, four had portal cirrhosis and one had pulmonary tuberculosis, brucellosis, and asymptomatic syphilis. All patients had sensorimotor polyneuritis, symptoms of the involvement of the lower extremities being present in all, and of the upper extremities in five patients. All complained of pain, which in two was so severe that it interfered with rest. In the first four patients, vitamin B_{12} was given first in daily doses of 50 mcg., but later the author used a uniform dose of 100 mcg. daily, and this dose was continued for from 12 to 36 days. All other medication was suspended during this time, as was the consumption of alcoholic drinks. The diet was the general hospital diet, care being taken that adequate amounts of proteins were included. All patients showed rapid subjective improvement. The pain and parasthesias subsided in a few days. Excellent objective improvement was obtained in seven, slight improvement in one, and no improvement in one. The author feels that vitamin B_{12} is an efficient therapeutic agent in alcoholic polyneuritis.

Alzheimer's Disease: A Clinico-Pathologic Analysis of 23 Cases with a Theory on Pathogenesis. L. Goodman. J. Nerv. & Ment. Dis. **118**:97-130 (Aug.) 1953.

Studies were carried out on 23 patients with Alzheimer's disease (presenile sclerosis) observed at a State Hospital at which the disease accounted for 3.1% of all autopsies. The average age at onset was 56 years. The average duration of illness was 6.8 years, with extreme variations of 8.5 months and 14 years. The author attempted to find clinical features that might serve as a clue to the pathogenesis, such as histogenetic and quantitative relationships between Alzheimer's cell disease and plaque formation. He hoped to learn whether Alzheimer's disease is a specific entity or merely a type of premature senescence, differing from senile psychosis only in its chronology. The major initial symptom was a disturbance in memory and associated confusion. Hallucinations, mostly of a visual nature, occurred in the majority of cases. Paranoid delusions were common early in the disease. The clinical diagnosis had been accurate in 13 cases, psychosis with cerebral arteriosclerosis being the most frequent diagnostic error. Histochemical and histological studies suggested two pathogenic possibilities. The first and most likely possibility is that it may be due to a disturbance in the cerebral metabolism of iron, resulting in secondary devitalization of the microglia. The second possibility is that there is a primary devitalization of the microglia that leads to the gradual accumulation of metabolic wastes in the nerve and macroglial cells producing their ultimate degeneration. In either case, Alzheimer's neurofibrillary degeneration and argentophilic plaque

formation seems to be due to microglial insufficieny, whether the latter is primary or secondary. The theory of microglial insufficiency or inhibition accounts for the origin of plaques from nerve cells as well as from macroglial and microglial cells. It affords a rational explanation for the apparent dissociation between plaques and Alzheimer cell changes. The study of a brain with Alzheimer's disease, six days after cerebral biopsy had been performed, indicated that the microglia in the tissue adjoining the biopsy lesion were capable of phagocytosis and of fat elaboration, which suggests inhibition rather than devitalization. The effects of antireticular cytotoxic serum in three cases of Alzheimer's disease were inconclusive, but they indicated a response of the microglial cells to the stimulation by antireticular cytotoxic serum. Significant clinical, pathological, and histochemical differences between Alzheimer's disease and senile dementia justify the conclusion that Alzheimer's disease is a metabolic syndrome that may occur independently of senile changes. There is no conclusive evidence that the disease is a premature form of senescence, even though it occurs predominantly during the so-called presenium. The author believes that the pathogenesis of Alzheimer's disease will not be clarified until further biochemical studies are carried out.

PEDIATRICS

Exchange Transfusion Results in Erythroblastotic Infants. R. Katzenstein and A. J. Ryan. Connecticut M. J. **18:**210-215 (March) 1954.

Of 32 infants with erythroblastosis who were born alive at the Meriden Hospital, 19 were given exchange transfusions, but 5 of these 19 died. Follow-up studies on the 14 children who received exchange transfusions and survived the neonatal period from three months to five years revealed that 2 children are alive with spastic disease and one died of acute leukemia at the age of 18 months. The development was satisfactory in the other 11 children. The authors found that the level of the mother's anti-Rh titer does not provide a definite prognostic sign of the development of erythroblastosis in the infant. There were two children with comparatively low maternal titers (32 and 64), who died in spite of exchange transfusion. There were three children whose maternal titers were relatively high (up to 1:1,024) who did not show clinical evidence of severe erythroblastosis. These children are alive and well and on reexamination were found to be Rh positive. Another child with a high maternal titer received no therapy, but secondary anemia subsequently developed. The maternal titers of the other children who died in spite of exchange transfusion were very high (from 5,200 to 100,000) and were proportional to the anemia. In none of the children who survived, either with or without therapy, was the nucleated red blood cell count over 20,000. A hemoglobin figure below 12 gm. and a nucleated red blood cell count above 20,000 indicate a very unfavorable prognosis.

Case of Rh Incompatibility and Deformities in Successive Infants. M. Brenner. Geburtsh. u. Frauenh. **14:**150-153 (Feb.) 1954. (In German.)

Brenner presents a family history of interest in connection with the question of a possible connection between Rh incompatibility and deformities in the offspring. The woman's first child, whose father was not her present husband, was normal. The first of the six children by the present husband was a girl who died of jaundice two weeks after birth. The following year a boy was stillborn, and two years later another boy was born who was well. A year later another girl was born with generalized hydrops, microcephaly, and micromelia. Two years later another healthy boy was born, but another pregnancy nine years later terminated in abortion during the fourth month, and the aborted fetus showed signs of deformity. Rh incompatibility was thought of and examination revealed that the husband had blood group B, Rh-positive and the wife A, Rh-negative. The titer of blocking antibodies was 1:64. This and higher titers are regarded as unfavorable. The author feels that although endogenic-hereditary causes may play a part in individual cases of deformities in a series of births involving Rh incompatibilities, a repetition of births with deformities and associated with erythroblastic disorders, definitely suggests a common cause, that is, the effect of an Rh antigen-antibody reaction on the fetal tissues.

Sclerema Adiposum Neonatorum: Cure Following Treatment with Cortisone. K. C. M. Fauser. Nederl. tijdschr. geneesk. **98:**549-555 (Feb. 27) 1954. (In Dutch.)

Fauser reports on a prematurely born pair of monozygotic twin boys in whom livid, hard spots appeared on legs and arms 24 hours after delivery. After consultation with a dermatologist, the disorder was diagnosed as sclerema adiposum neonatorum. Treatment with corticotropin (ACTH) produced hardly any improvement. Next, oral administration of cortisone was given and followed by rapid improvement. Both infants were in excellent health when reexamined at 5 months of age. The mother of these twins had a myomatous uterus, and it is assumed that this may have contributed both to the premature delivery of the twins and to the development of the sclerema. The author discusses possible reasons for the failure of the corticotropin and the success of the cortisone treatment. He cites from literature another case of sclerema adiposum neonatorum in which treatment with cortisone proved effective.

Idiopathic Spontaneously Occurring Hypoglycemia in Infants: Clinical Significance of Problem and Treatment. I. McQuarrie. A. M. A. Am. J. Dis. Child. **87:**399-428 (April) 1954.

Forty children with spontaneously occurring hypoglycemia were admitted to the pediatric service of the University of Minnesota Hospitals during the past 12 years. The cause of the hypoglycemia was determined in 15, while the remaining 25 (62.5%) presented a persistent hypoglycemia of unknown cause (syndrome of idiopathic hypoglycemia). The age at the time of onset of hypoglycemia in these 25 patients was one of its striking features. In 21 of the 25 it occurred before the age of 2 years, and 19 patients were between the ages of 3 and 18 months, hence the use of the term infantile. In only one child did the onset of demonstrable hypoglycemia occur after the age of 5 years. Of the 25 patients with idiopathic hypoglycemia, there were 18 boys and 7 girls. Eleven of the 25 had brothers or sisters with the same type of hypoglycemic disorder, thus exhibiting a familial or genetic trait the high incidence of which was a striking characteristic in the series of patients reported on. The family histories of the other patients indicated the probable occurrence of the syndrome in a previous generation. All 25 patients were well within the normal range of weight and anthropometric measurements. Dietary and other nutritional or metabolic factors were normal. The signs and symptoms of the hypoglycemic episodes appeared entirely like those occurring spontaneously in other hypoglycemic states and not unlike those resulting from insulin overdosage in diabetic patients. The definite diagnosis of idiopathic infantile hypoglycemia requires differentiation from certain better-known endocrine and metabolic disorders in which spontaneous hypoglycemia may constitute an important clinical feature. The commonest of these are adrenocortical insufficiency (Addisonian type), anterior pituitary insufficiency, true hyperinsulinism due to pancreatic (beta cell) hyperplasia or tumor of the islets of Langerhans, liver insufficiency (such as congenital cirrhosis, extreme fat deposition, von Gierke's glycogen storage disease, galactosemia), and severe hypothyroidism (infantile myxedema, cretinism). The absence of physical stigmas and normal responses to all special tests, except those immediately related to glucose and insulin tolerance, characterize the cases of idiopathic infantile hypoglycemia. No genuine case of this disorder, so far tested, failed to respond to treatment with corticotropin. Hormone therapy in severe cases should be instituted without delay so that brain damage may be avoided. Corticotropin, in proper doses, acts much like a specific agent, but there is no other evidence of hypopituitarism. A simple empirical rule is to initiate treatment with plain corticotropin (ACTH) intramuscularly at the rate of 4 mg. per kilogram of body weight (or 100 mg. per square meter of body surface) per day, given in four equal doses at six hour intervals for four days. For the following week, one-fourth of this dose is given night and morning in the form of highly purified corticotropin-gel (Acthar-gel). The morning dose is omitted during the succeeding few weeks, if

the fasting blood sugar remains normal with this dosage schedule. The criteria for guidance during extended periods of treatment are maintenance of a symptom-free state and fasting blood sugar levels above 40 mg. per 100 cc. Dosage of the corticotropin must be adjusted on an individual basis. Of 11 patients in whom a similar schedule of corticotropin was employed, 4 improved sufficiently to permit discontinuance of such therapy after variable periods of time without return to hypoglycemia. Other patients in the group treated were maintained in an essentially normal state by use of as little as 5% of the original daily dosage. Very much larger doses of cortisone or hydrocortisone by mouth are required for maintenance, if this is substituted for the corticotropin.

The Treatment of Pinworm Infection (Enterobiasis): A Comparative Study of Three Oxyuricides. T. S. Bumbalo, F. J. Gustina and R. E. Oleksiak. J. Pediat. **44**:386-391 (April) 1954.

Of 155 children with pinworm infection treated with one of three oxyuricides, 47 were treated with piperazine hexahydrate, 50 were treated with oxytetracycline (Terramycin), and 58 were treated with dehydrated garlic powder. Piperazine hexahydrate was administered in the form of a palatable 10% syrup containing 100 mg. of the drug per cubic centimeter; patients between the ages of 1 and 5 years were given half a teaspoon three times a day, those between the ages of 5 and 10 years received one teaspoon three times a day, and those over 10 were given one and a half teaspoons three times a day. Of the 47 patients who were treated for seven days, rested for seven days, and then treated for seven more days, 40 had seven consecutive negative post-treatment cellulose (Scotch) tape swab smears, while the remaining 7 patients had one to seven positive post-treatment smears. The cure rate in this group of patients was 85%. Results obtained confirmed those of White and Standen, who reported that piperazine hexahydrate is a nontoxic, safe, and effective oxyuricide. Cures were obtained in only 4 (7%) of the 58 patients who were given 8 grains (50 gm.) of dehydrated garlic powder three times daily (a total daily dose of 24 grains [150 gm.]) for seven days, rested for seven days and then treated for seven more days. The percentage of cures in this group was the lowest of nine oxyuricides tested by the authors. Because of the ancient reputation of garlic as a "popular remedy" for pinworm infection, substantiated in part by medical research, and because of the possibility that some active principle of garlic was lost in the dehydration process and that the bottles containing the garlic syrup were not carefully shaken before a dose was administered, the authors believe that garlic should be given additional therapeutic trials by them and by other workers after some of the details of the dosage of dehydrated garlic powder have been confirmed. The complete lack of toxicity and the low cost of dehydrated garlic powder would make it an ideal oxyuricide if repeated studies should confirm the high cure rates obtained by other workers. Oxytetracycline in a reduced dosage of 5 mg. per pound of body weight divided into three daily doses, given in two seven day courses with a seven day interval between the two courses, cured only 19 (38%) of the 50 patients treated with it. This dosage, one-half of the amount the authors reported on in an earlier study, apparently is not enough to produce an effective cure rate. Since the syrup of piperazine hexahydrate used by the authors was easy to take, is well tolerated, and can be made available inexpensively, they believe that piperazine hexahydrate comes the closest to their standard of an ideal oxyuricide.

UROLOGY

Renal Papillary Necrosis. D. Swartz. J. Urol. **71**:385-397 (April) 1954.

Renal papillary necrosis, known also as renal papillitis, medullary necrosis, papillitis necroticans, and necrotizing papillitis, is an ischemic necrotic lesion of the renal papillae that occurs in patients with chronic urinary obstruction with or without diabetes. Most cases were discovered at necropsy. Swartz reports on two patients with advanced unilateral renal lesions who recovered after nephrectomy. The third patient, a 15-month-old girl, was hospitalized because of persistent temperatures ranging from 103 to 108 F. An exploratory craniotomy for a suspected subdural hematoma revealed no such lesion, but a diffuse cerebral atrophy. Autopsy disclosed Pseudomonas aeruginosa meningitis, moderate cerebral atrophy, and other intracranial lesions, the cause of which was not understood. Bilateral renal papillary necrosis was discovered, although it was not suspected during life. In diabetic patients, the clinical manifestations may be acute or subacute. In the acute form of the disease, there is rapid onset of illness with chills, fever, prostration, rapid pulse, leukocytosis coma, pyuria, hematuria, and oliguria. Death is due to infection and uremia. Prolonged pyelonephritis with remissions and exacerbations characterize the subacute condition. The diabetic state is difficult to control and the patient may lapse into coma. There may be ureteral colic due to passage of necrotic tissue through the ureter. The sudden development of severe diabetic acidosis, a rising blood urea, and general deterioration portend the onset of the terminal state. The pyelographic aspects may simulate renal tuberculosis or nontuberculous pyelonephritis. A moth-eaten appearance of the minor calyces results from necrosis and sloughing of the renal papillae. In advanced cases, extravasated contrast medium may extend into the renal cortex. A portion of a pyramid that has sloughed away and floats free in the renal pelvis may cast a negative shadow suggesting a nonopaque stone. A great variety of bacterial agents have been isolated in cases of this type; the commonest offender being Escherichia coli, but Staphylococcus aureus, Klebsiella pneumoniae (Friedlander's bacillus), Bacillus proteus, alpha and beta streptococci, and P. aeruginosa have also been found. The lesion must be differentiated from renal tuberculosis, acute destructive pyelonephritis, renal tumors, and renal colic due to stone. Control of the diabetic state and frequent search for urinary infection may prevent this serious complication, and surgical treatment of obstructive uropathy will prevent this condition in the aged. The proper treatment is that of urinary infections, employing chemotherapeutic and/or antibiotic measures. Nephrectomy was justified in the two reported cases because of advanced unilateral renal lesion with massive destruction and gross infection. Papillary necrosis may occur in association with pyelonephritis, with vascular occlusion or as an isolated lesion. It is not possible to explain the pathogenesis of all forms of this disease.

Nephrocalcinosis: A Collective and Clinicopathologic Study. J. D. Mortensen and J. L. Emmett. J. Urol. **71**:398-406 (April) 1954.

Deposits of calcium salts in renal parenchyma are demonstrable histologically in from 5 to 25% of all kidneys subjected to careful postmortem examination, but in the living patient it was not reported until 1934, when Albright and associates described the roentgenographic manifestations of calcium deposits in the kidneys of patients with primary hyperparathyroidism and coined the term, "nephrocalcinosis." Mortensen and Emmett collected 48 cases from the medical literature and 43 cases from the files of the Mayo Clinic. The primary disorder responsible for nephrocalcinosis is recognizable clinically in approximately 84% of the cases. Primary hyperparathyroidism, hyperchloremic acidosis, and chronic pyelonephritis are responsible for 75% of the cases. Less common causative disorders are chronic glomerulonephritis, recurrent "idiopathic" renal lithiasis, and "idiopathic" hypercalciuria. There are no characteristic symptoms or physical findings attributable to nephrocalcinosis; its clinical recognition depends on its roentgenographic demonstration. The clinical evaluation of the patient with nephrocalcinosis requires the determination in the blood of the concentration of calcium, phosphorus, carbon dioxide combining power, chlorides, and urea or nonprotein nitrogen. Interpretation of the results of these determinations usually indicates the nature of the primary disorder. Deposits of calcium primarily in medullary regions in relation to collecting tubules and chronic inflammatory changes in medullary interstitial tissues are the characteristic pathological lesions of nephrocalcinosis. Degenerative changes, including large areas of destruction, replacement with calcareous deposits, cystic dilation and deformity of tubules, and cicatrization, are frequently observed in such kidneys. None of these gross or histological changes are pathognomonic of roentgenographically demonstrable nephrocalcinosis, and any or all may be present in kidneys that do not cast

roentgenographic shadows that can be interpreted as nephrocalcinosis. Early recognition and prompt eradication of the primary causative disorder before advanced renal insufficiency has developed offer patients with nephrocalcinosis the best chance for postponing or avoiding fatal uremia.

THERAPEUTICS

Death from Hypersensitivity Due to Phenylbutazone. D. J. O'Brien and G. Storey. Brit. M. J. **1**:792-794 (April 3) 1954.

The clinical and necropsy findings in a patient dying from a generalized hypersensitivity reaction during phenylbutazone treatment of rheumatoid arthritis are described. The hypersensitivity reaction was histologically demonstrated by three types of lesion—polyarteritis nodosa, hypersensitivity angiitis, and granulomatous lesions, the two latter predominating. Such a condition should be considered when the appearances at necropsy are indefinite in fatalities during this therapy.

Stevens-Johnson Syndrome and Granulocytopenia After Phenylbutazone. S. J. Steel and J. L. Moffat. Brit. M. J. **1**:795 (April 3) 1954.

A severe case of sensitivity to phenylbutazone is described. The features were those of Stevens-Johnson syndrome and granulocytopenia. Penicillin and diphenhydramine hydrochloride, but not cortisone or corticotropin, were used in treatment. The patient made an uneventful recovery.

RADIOLOGY

Reliability of Brain Tumor Localization by Roentgen Methods. F. J. Hodges, J. F. Holt, R. C. Bassett and L. J. Lemmen. Am. J. Roentgenol. **71**:624-631 (April) 1954.

Study of the results obtained by various methods of preoperative roentgenologic examination in patients with brain tumors seen at the University Hospital (Ann Arbor) during the 10 year period from July 1, 1941, to June 30, 1951, shows that they have greatly increased the ability to determine the location of such tumors within the skull. Localization arrived at on the basis of detailed neurological examination proved accurate in 60.5% of the cases, and, since this method presents no hazard to the patient, it should be used to the fullest extent. Electroencephalography, which is also nontraumatizing, often yields valuable diagnostic information. Roentgenologic skull survey is likewise harmless and easy to carry out and should be widely used, because it provides conclusive evidence of the location and sometimes of the character and size of certain intracranial tumors (oligodendroglioma, chromophobe adenoma of the pituitary, and craniopharyngioma). Pneumoencephalography, though subject to many restrictions, can often be used very effectively in the case of tumors involving the brain surface, especially at the base, where other methods are apt to fail. Cerebral angiography is less traumatic to the patient than ventriculography and has certain specific fields of usefulness, but it should not be employed if there is reason to suspect that the tumor lies in the posterior fossa. Ventriculography, though the best of the specialized methods both in individual accuracy and actual utility, is also the most disturbing and hazardous for the patient and must often be followed promptly by craniotomy, because of the dramatic effects sometimes produced by the change in hydrodynamics within the cranial vault. Its value depends on the skill and experience of the investigator, but, when used by a capable examiner in a group of patients with intracranial tumors of all sorts, it may be expected to provide accurate localizing signs 9 times out of 10.

A Correlation of Roentgen and Surgical Findings in 200 Cases of Rheumatic Mitral Valvular Disease: Evaluation of Cardiac Chamber Size, Valvular Calcification and Pulmonary Vessels. J. S. Lehman and J. L. Curry. Am. J. Roentgenol. **71**:599-612 (April) 1954.

The recorded surgical observations of 192 patients operated on for the relief of mitral stenosis and 8 others operated on for the relief of mitral insufficiency were studied in an attempt to evaluate the reliability of roentgen studies in assessing cardiac chamber enlargement, mitral valvular calcification, and the size of the pulmonary vessels. Examination of the right atrium during mitral valve operations is not possible with the left thoracic approach used in these patients; consequently, correlative data in regard to its size were not available. Roentgenologic estimation of right atrial size presents numerous difficulties necessitating caution before a finding of enlargement can be arrived at. Little difficulty, however, will be encountered in making an accurate prediction of right ventricular enlargement, although angiocardiography may be needed to determine the extent to which the prominence of this chamber depends on the displacing effect of an enlarged left atrium. Esophageal displacement is perhaps the most measurable evidence of left atrial enlargement. The degree of carinal widening is usually parallel to both the magnitude of the enlargement and the degree of esophageal displacement. No correlation could be found, however, between the shape of the displaced bronchi and the degree of left atrial enlargement. Posterior esophageal displacement caused by left atrial enlargement usually ends well above the diaphragm, but some of the larger left atriums in this series extended downward and intruded into the posteroinferior cardiac recess. Obliteration of the posteroinferior cardiac recess by factors other than left ventricular enlargement and inability to identify the so-called interventricular notch have added to the difficulty of predicting left ventricular size. The position of the left cardiac apex proved to be the most reliable single guide in assessing the size of this chamber. Surgical exploration showed a high degree of roentgenologic detection of mitral valve calcification in these patients. Roentgenologic predictions, however, usually underestimated the size of the major pulmonary vessels, partly perhaps as a result of masking by features of cardiac enlargement. The difficulties encountered in roentgenologic attempts to determine the presence and degree of mitral insufficiency render their value problematical.

Nine Cases of Irradiation Damage to Anterior Wall of Chest: Fatal Outcome in One Case. R. Birkner and J. Schaaf. Strahlentherapie **93**:454-465 (No. 3) 1954. (In German.)

Birkner and Schaaf present histories of nine patients who sustained irradiation damage of the chondro-osseous chest wall. The majority of these patients were women who had received postoperative irradiation following breast resection for carcinoma. The group also included one man with mammary carcinoma and two men with bronchial carcinoma. Spontaneous rib fractures and damage to the cartilages, skin, and other soft tissues were delayed in some cases as long as 10 years; in others the interval ranged from 6 months to 7 years. Data on the sites of lesions, fields irradiated, type of irradiation, estimated focal doses, and effective bone doses are also reported. The authors feel that other unknown biological factors, such as individual variations in sensitivity of the bones to irradiation, might play a contributing part.

Progressive Exophthalmos Following Thyroidectomy Cured by Irradiation of Cerebral Centers: Case Report. A. T. Berkman. Radiology **62**:406-408 (March) 1954.

Berkman resorted to irradiation of the hypophyseal-hypothalamic region in a case of severe exophthalmos showing continuous progression two and a half years after thyroidectomy. The exophthalmos promptly diminished, and other symptoms of sympathetic origin disappeared.

Osteogenic Sarcoma in Muskrat from Area of High Environmental Radiostrontium. L. A. Krumholz and J. H. Rust. A. M. A. Arch. Path. **57**:270-278 (April) 1954.

A muskrat (Ondatra zibethica) was captured by guards of the Oak Ridge National Laboratory who observed that the animal's right hind leg was largely useless. The animal was killed on the day following its capture. A large tumor was seen extending from the knee joint to near the distal end of the tibiofibula. On microscopic examination the tumor was diagnosed as a sclerosing type of osteogenic sarcoma of the right tibiofibula, with metastases to the lungs and kidneys. Although most of the soft tissues of the body were sampled, none of them contained amounts of radioactive materials that could have had harmful effects. The bone, toenails, and trachea contained unusually large amounts of radioactivity. Absorption curves

based on the data from the samples of the left metatarsal and the right femur indicated that the radioactive material present in each was largely radiostrontium (Sr^{90}) and its daughter product radioyttrium (Y^{90}). It was estimated that the entire skeleton of the muskrat contained nearly 100 μc. of radioactive strontium. The bony tissue of the muskrat probably received a constant dose of at least 1.5 rep per hour (40 rep per day). The duration of the exposure to the bones of the muskrat was not known. In the area in which the animal was found there is an abundance of food plant material containing large amounts of radioelements. The plants appear healthy, and it seems that they are capable of concentrating the various radioelements in amounts and percentages that are considerably different from those occurring in the water in which they were growing. It is highly probable that the osteogenic sarcoma arose in the muskrat because of the carcinogenic action of the radiostrontium contained in the bone.

Mortality in Swine Exposed to Gamma Radiation from an Atomic Bomb Source. J. L. Tullis, B. G. Lamson and S. C. Madden. Radiology **62:**409-415 (March) 1954.

Ninety swine 4 to 6 months old and weighing an average of 67.2 pounds were divided into nine groups of 10 each, randomized according to weight in such a manner that the weight distribution was the same at each of the nine test stations. On the morning before irradiation, the swine were identified by number and loaded into the liners of exposure cages specially designed to protect them from all atomic bomb energies except ionizing radiations. They were then placed in the firmly anchored cylindrical exposure cages at the nine target stations. At seven of the stations there were five males and five females, but at station 4 there were 10 males and at station 7 there were ten females. The sex distribution at stations 4 and 7 was fortuitous and did not apparently influence the experimental results. Ionizing radiation from an atomic bomb was sufficient to kill all swine receiving between 320 and 1,000 r. Eight of 10 swine that received 275 r died on or before the 19th day after exposure; 2 survived for 30 days, at which time they were killed for study. Two of 10 swine that received 180 r died on or before the 17th day after exposure, but the remaining 8 survived for 30 days, at which time they were killed. By calculation, 100% of the swine would be expected to die when irradiated with 390 r, 50% would be expected to die when irradiated with 230 r, and 100% would be expected to survive when irradiated with 130 r. The experimental data agree closely with the calculated expected results and, when the variables are taken into account, with previous 2,000 kv. (peak) x-irradiation control studies.

PHYSIOLOGY

Correlation Between Capillary Resistance and Circulating Eosinophils. J. Kramár, V. W. Meyers and D. J. Peetz. J. Lab. & Clin. Med. **43:**395-405 (March) 1954.

Recent clinical observations and experimental work suggest that capillary resistance not only is a local phenomenon but is subject to hormonal regulation. The adrenal cortex is principally involved and cortisone is its mediator. Since the level of the circulating eosinophils, or better, its change on induced cortical activation, is considered to be a reliable and feasible indicator of adrenocortical activity, the correlation between the capillary resistance and the eosinophils was studied and their respective values in the assessment of adrenocortical function were compared. The following experimental conditions were chosen for this study: (1) adrenalectomy in the normal rat; (2) administration and withdrawal of cortisone in the rat after adrenalectomy; (3) prolonged administration of cortisone in rats and dogs after such surgery; (4) prolonged administration of cortisone to a normal dog; (5) forced muscular exercise in a normal rat; (6) cold stress in a normal rat; and (7) prolonged fasting in a normal dog. A good inverse correlation was found in any situation presumably connected with a change in cortisone concentration of the body. 1. If cortisone concentration increases (cortisone administration to normal or to animals having had adrenalectomy, first phase of stress response presumably associated with corticotropin discharge) the capillary resistance rises and the eosinophils drop. 2. If the cortisone level decreases (cortisone withdrawal in normal or in animals having had adrenalectomy, adrenalectomy in normal rat, second phase of stress response presumably connected with cortical hypofunction) the capillary resistance precipitously drops and eosinophilia occurs. A good inverse correlation (persistent high capillary resistance and persistent low eosinophil level) was found in any situation in which a high cortisone level was maintained during a long period of time by either exogenous (cortisone administration) or endogenous (protracted stress) method. No persistent correlation was found in any situation connected with a permanently low cortisone level in the animals. After adrenalectomy or withdrawal of cortisone there is at first a seesaw movement; the capillary resistance drops and eosinophilia sets in. This good correlation fades, however, when the cortisone level remains low in that the high eosinophil count returns to normal levels, whereas the capillary resistance remains permanently low. In these conditions the eosinophils cease to reflect the cortisone level, and only the capillary resistance remains as a reliable indicator. Capillary resistance seems to be regulated mainly by cortisone, whereas the level of circulating eosinophils is dependent on a variety of factors, cortisone being only one of them. Even if the mechanism of the depressant action of cortisone on the eosinophil count is not clearly understood, there is doubt that this action is a positive function of cortisone. The effect of any decrease in cortisone concentration on the eosinophils must, therefore, be considered as a negative function. It seems that the depressant action of cortisone is so predominant that in its presence no other regulatory factors can become effective or manifest. When the depressory action of cortisone decreases, the resulting eosinophilia is likely to be compensated and the high count brought down to normal by some of these factors.

The Anurias Following Kidney Transplantation. W. J. Dempster. Acta med. scandinav. 148:91-100 (No. 2) 1954. (In English.)

There are four types of anuria following autotransplantation and homotransplantation of kidneys in dogs. Type 1 is the failure to secrete after the establishment of the new circulation. Type 2 is an anuria following a period of poor secretion and associated with the toxic syndrome, manifesting itself any time between 24 and 48 hours after transplantation. Type 3 is an anuria occurring in homotransplanted kidneys at a varying interval after transplantation and following a period of good secretion. It occurs in the first kidneys to be transplanted and is rapid in onset. It is assumed to be the result of an antigen-antibody reaction. Type 4 is an anuria that occurs within a few hours after transplanting the second kidney from the same donor to the same recipient that received the first. It follows a few hours of secretion and is associated with severe and widespread disintegration of the renal parenchyma. It also appears to represent a severe antigen-antibody reaction. This paper is concerned with some cases of type 1 that occurred in the author's three year experience. The anuria is quite unpredictable. An immunological factor does not appear to be involved, since the anuria occurred in autotransplants as well as in homotransplants, but this possibility is not excluded. There were 18 type 1 cases in autotransplanted and 16 in homotransplanted kidneys. The period of ischemia involved in transplanting the kidneys was about 20 minutes. In the kidneys removed 36 to 48 hours after transplantation, which included all the autotransplants and 12 of the homotransplants, three histological types were noted. They were (1) generalized cloudy swelling of the tubule cells and a few casts in the distal tubules and collecting tubules (8 autotransplants and 2 homotransplants); (2) universal or focal necrosis sometimes associated with interstitial edema and/or casts in the distal tubules (4 autotransplants and 6 homotransplants); and (3) widespread casts in both proximal and distal tubules associated with empty, dilated distal tubules (6 autotransplants and 4 homotransplants). Four homotransplanted kidneys were left in the animals for from three to five days. Arteriograms were taken of seven kidneys with injection of tolazoline (Priscol); the drug exerted a vasoconstricting effect, contrary to expectation. Arteriolar spasm, which may be initiated by direct nervous irritation during removal of a kidney, and damage to the filtering mechanism are suggested as possible causes of type 1 anuria.

BOOK REVIEWS

Prematurity, Congenital Malformation and Birth Injury. Proceedings of conference sponsored by Association for Aid of Crippled Children at New York Academy of Medicine, 2 E. 103rd St., New York 29, June 5 and 6, 1952. Co-chairmen: Dr. L. Emmett Holt, Jr., Dr. Theodore H. Ingalls, and Dr. Louis B. Hellman. Cloth. $4. Pp. 225, with illustrations. Association for Aid of Crippled Children, 345 E. 46th St., New York 17, 1953.

In the field of prematurity, the subjects covered in this book include respiratory exchange, immunology, hematology, the development of enzyme systems, endocrinology, and the prevention of premature births. The section on congenital malformation includes discussions of principles underlying experimentally induced anomalies, cleft palate induced in rats by cortisone, the effect of amino acid analogues on the development of the explanted chick embryo, clinical classes of malformation during prenatal life, traumatic abortion and prenatal death of the embryo, mass study of reproductive wastage, and the statistical approach to the study of congenital malformations. The following subjects are covered in the section on birth injury: clinical impact of late pregnancy hemorrhage, the pathology of late pregnancy hemorrhage, pathological changes in the infant in anoxia, placental transfer of oxygen, fetal tolerance of anoxia, and transverse narrowing of the pelvis as a cause of dystocia. In addition to the main papers there are interesting discussions by other experts. This book should be read carefully by obstetricians, pediatricians, pathologists, epidemiologists, embryologists, and by many orthopedists and social service workers. The publishers have done their part most ably.

Traité de médecine. Publié sous la direction de M. Pr A. Lemierre, et al. Secrétaires généraux: A. Ravina et J. Patel. Tome I: Maladies infectieuses (première partie). Par Arnaud, et al. Cloth 2200 francs. Pp. 1096, with 83 illustrations. 1947. Tome II: Maladies infectieuses (seconde partie); maladies parasitaires. Par Audry, et al. Cloth. 1950 francs. Pp. 956, with 198 illustrations. 1947. Tome III: Tuberculose, cancer, maladie de Besnier-Bœck-Schaumann, syphilis. Par J. Bretey, et al. Cloth. 3600 francs. Pp. 910, with 300 illustrations. 1951. Tome IV: Avitaminoses; intoxications; maladies par agents physiques; anaphylaxie; accidents sériques. Par E. Aujaleu, et al. Cloth. 2100 francs. Pp. 895, with illustrations. 1948. Tome V: Maladies de l'appareil respiratoire. Par Bérard, et al. Cloth. 2400 francs. Pp. 1165, with 164 illustrations. 1948. Tome VI: Tuberculose pulmonaire. Par M. Bariéty, et al. Cloth. Pp. 558, with illustrations. 1952. Tome VII: Maladies du tube digestif et de ses annexes. Par M. Aussannaire, et al. Cloth. 2300 francs. Pp. 1063, with illustrations. 1948. Tome VIII: Maladies du foie et du pancréas. Par M. Albeaux-Fernet, et al. Cloth. 2500 francs. Pp. 1166, with illustrations. 1948. Tome IX: Maladies de la nutrition. Par R. Boulin, et al. Cloth. 2400 francs. Pp. 854. 1949. Tome X: Maladies du cœur. Par M. Bérard, et al. Cloth. 3600 francs. Pp. 1167, with illustrations. 1948. Tome XI: Maladies des vaisseaux. Par M. Bérard, et al. Cloth. 1400 francs. Pp. 545, with illustrations. 1948. Tome XII: Maladies du sang et des organes hématopoiëtiques. Par C. Albahary, et al. Cloth. 2400 francs. Pp. 727. 1949. Tome XIII: Maladies des glandes endocrines. Par Albeaux-Fernet, et al. Cloth. 2600 francs. Pp. 1119, with illustrations. 1948. Tome XIV: Maladies des reins. Publiésous la direction de Pasteur Vallery-Radot, professeur à la Faculté de médecine de Paris, avec la collaboration de P. Delafontaine, et al. Cloth. 2800 francs. Pp. 920, with illustrations. 1949. Tome XV: Maladies du système nerveux, première partie. Par A. Ajuriaguerra, et al. Cloth. 3400 francs. Pp. 1254, with illustrations. 1949. Tome XVI: Maladies du système nerveux, seconde partie. Par J. A. Barré, et al. Cloth. 3400 francs. Pp. 1251, with illustrations. 1949. Tome XVII: Maladies des muscles, des os, des articulations. Rhumatismes. Par P. Chiche, et al. Addenda aux tomes I, II, IV, V, XII et XVII. Par A. Aschkénasy, et al. Table alphabétique des tomes I à XVII. Cloth. 6100 francs. Pp. 1061, with illustrations. Masson & Cie, 120 boulevard Saint Germain, Paris, 6e, 1953.

This new and encyclopedic reference work on internal medicine is by a distinguished group of contributors that includes many well-known professors in France, Belgium, and Switzerland. It is a modern replacement of the well-accepted and much-used systems of medicine prepared by Roger, Widal, and Teissier about 25 years ago. The profound changes in scientific medicine have necessitated a complete rewriting. These volumes should be of value to the internist, general practitioner, and student.

The first two volumes review in detail the infectious diseases. The third is devoted mainly to tuberculosis and syphilis, with a smaller section on cancer. Vitamins are reviewed in the fourth volume, with discussions on avitaminosis, industrial poisons, toxic agents, and the effects of physical, chemical, and biological agents on the body. Diseases of the upper air passage, trachea, bronchi, lungs, pleura, and mediastinum are discussed in the fifth volume. The sixth is devoted to a review of pulmonary tuberculosis. Diseases of the esophagus, stomach, duodenum, colon, rectum, salivary glands, and peritoneum are described in the seventh. The liver, bile ducts, gallbladder, and pancreas are covered in the eighth volume. Metabolic disorders, including obesity, diabetes insipidus, diabetes mellitus, and gout, are discussed in the ninth. The 10th is devoted to diseases of the heart and the 11th to diseases of the blood vessels. Hematology and splenic diseases are discussed in the 12th volume and endocrine disorders in the 13th. Diseases of the kidneys are the subject of the 14th. The next two volumes are devoted to the diseases and disorders of the nervous system, and the last volume discusses the muscles, bones, and joints and rheumatic diseases.

The detailed review of each disease follows a pattern of a brief historical account, etiology, microbiology when applicable, pathological changes, clinical findings, variations in clinical types, diagnosis, differential diagnosis, prognosis, prophylaxis, and treatment. A number of helpful, introductory chapters review the disease, the disturbed physiological processes involved, methods of examinations, laboratory findings, and pathogenesis. They should give the reader a grasp of the disease processes and the factors involved. The carefully worded descriptions of disease entities and numerous variations of clinical entities should be especially useful to those who are confronted with atypical forms of disease. Diagnosis and laboratory findings are presented clearly and in detail. Unfortunately, there are wide variations in the recommended methods of treatment. Some chapters contain recent references to antibiotics and newer biological and chemical forms of treatment, while others do not include the more recent innovations that have become accepted in the United States. For example, in the treatment of meningococcic meningitis, there is but brief mention of penicillin; tetanus toxoid is scarcely mentioned as a prophylactic measure; dihydrostreptomycin is not included in the treatment of brucellosis; and the use of radioactive iodine is not included in the treatment of hyperthyroidism. Many chapters contain valuable information drawn from the author's experience that makes an important addition to the medical literature.

The books are printed on good paper and are well bound. A pleasing type face has been used. Historical accounts of diseases, introductory statements, direct quotations from the literature, reports of atypical cases, and other items appear in a smaller though easily read type. Illustrations are used throughout the system; some authors have employed them to greater advantage than others. It is regretted that electrocardiograms are limited to the three conventional leads. The articles are well written generally, though there is some variation of style from author to author. The inclusion of broad physiological principles, recent laboratory findings, and factors concerned in pathogenesis add to the value of this series.

Stories on Stone: A Book of American Epitaphs. By Charles L. Wallis. Cloth. $5. Pp. 272, with illustrations. Oxford University Press, 114 Fifth Ave., New York 11, 1954.

One way to obtain an intimate sense of the American past is to walk through a quiet country graveyard, perusing the inscriptions on the tombstones. On old tombstones can be found comments on life, immortality, dreams, hopes, despair, joys, and frustrations. Another method of familiarizing oneself with stories on stone is provided by this book, which affords an interesting approach to a comprehensive collection of curious, humorous, and historically significant American tombstone inscriptions. More than 750 inscriptions are described, and these have been

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taken from all 48 states. These epitaphs, by turn ribald and ridiculous, pompous and lugubrious, eloquent, or serenely simple, show as nothing else the vitality and diffuse richness of American history and manners. Reading about them will convince the reader that his time has been well spent.

Essentials of Nursing. By Helen Young, R.N., and Eleanor Lee, A.B., R.N., Assistant Professor of Nursing, Department of Nursing, College of Physicians and Surgeons, Columbia University, New York. Edited by Helen F. Pettit, R.N., M.A., Assistant Professor of Nursing (Nursing Arts), Department of Nursing, Faculty of Medicine, Columbia University. Associate editor: Ruth A. Lynch, M.A., R.N., Instructor in Nursing, Department of Nursing, Faculty of Medicine, Columbia University. Foreword by Eleanor Lee. Third edition. Cloth. $4. Pp. 527, with illustrations by Mrs. Helen B. Pristop. G. P. Putnam's Sons, 210 Madison Ave., New York, 1953.

This book was compiled and written by the faculty of the school of nursing of Presbyterian Hospital in New York. More than 80 faculty members have made various specialized contributions to a text that represents an outgrowth of classroom experiences. The book is intended to help the beginning student acquire basic skills leading to her development as a competent nurse. In preparing this edition many of the topics were rearranged to improve the sequence of presentation. In some instances deletions were made to achieve clarity and continuity and assure a better balance of chapter content. A new chapter on rehabilitation was included so that the student might appreciate the importance of initiating at the onset of illness steps that will lead toward recovery. Many new drawings replaced outmoded ones, and numerous improved halftones were introduced.

The book is divided into four parts. Part 1 is devoted to the interrelationship between the nurse, the patient, and the hospital; part 2 concerns basic nursing care; part 3 defines the role of the nurse in diagnostic and therapeutic procedures; and part 4 discusses special adaptations of basic principles of nursing care. Each chapter is followed by a bibliography and selected references. This book attempts to cover a tremendous amount of material. It would seem that more attention to stimulating an understanding of such basic information is desirable. Much of the book is devoted to a presentation of facts, with few techniques used to encourage an understanding of the role of the nurse in the various situations. This book may serve as a reference text.

Handbuch der mikroskopischen Anatomie des Menschen. Begründet von Wilhelm v. Möllendorff. Fortgeführt von Wolfgang Bargmann. Band 6: Blutgefäss- und Lymphgefässapparat innersekretorische Drüsen. Teil 5: Die Nebenniere—Neurosekretion. Bearbeitet von R. Bachmann, E. Scharrer und B. Scharrer. Paper. 342 marks. Pp. 1199, with 336 illustrations. Springer-Verlag, Reichpietschufer 20, (1) Berlin W. 35 (West-Berlin); Neuenheimer Landstrasse 24, Heidelberg; Göttingen, 1954.

Part 5 of volume 6 of the extensive German handbook on microscopic anatomy deals mainly with the adrenal and with neurosecretion. Both chapters are characterized by the most comprehensive handling possible of the subject, including not only conventional histology but also comparative anatomy, histochemistry, and functional considerations designated in the chapter on the adrenal as histiophysiology. The literature is completely reviewed in both chapters, and consideration of the German literature is dovetailed with reports from the world literature. The illustrations are well chosen. Most of them, especially in the first chapter, are from other publications. Many of them are drawings, and quite a few are in color. Both chapters are well written and well organized. In the chapter on the adrenal, full justice has been done to this tremendous, constantly enlarging field of knowledge. The chapter on neurosecretion deals with nerve cells, in man mainly in the hypothalamus, which act as agents of endocrine secretion and which thus represent the mediators between nervous and endocrine function. This field, to which the authors have already contributed much, should profit again by this compilation. This volume, like all the others of the Handbuch of Möllendorff, is a valuable and unusually complete source of information on either the adrenal or neurosecretion.

Ophtalmologie. Par Louis Guillaumat, ophtalmologiste de la Clinique nationale des Quinze-Vingts, avec la collaboration de Suzanne Schiff-Wertheimer, ophtalmologiste de la Clinique nationale des Quinze-Vingts, Guy Offret, professeur agrégé à la Faculté de médecine de Paris, et André Dubois-Poulsen, ophtalmologiste de la Clinique nationale des Quinze-Vingts. Collection médico-chirurgicale à révision annuelle. Directeur général: Pasteur Vallery-Radot. Secrétaire général: Jean Hamburger. Cloth, loose-leaf. Pp. 1263, with illustrations. Ernest Flammarion, 22 rue de Vaugirard, Paris, 6e, 1953.

This is a loose-leaf book *in statu nascendi* written by four well-known French ophthalmologists. It seems to be intended for the younger ophthalmologist who is already familiar with the basic principles and phenomena of his field. The book covers the subjects dealt with in any textbook of ophthalmology. The relations of ocular to general diseases are emphasized and are discussed in greater detail than in many other texts. A shortcoming is the limited number of pictures. Pictures of the various normal types of ocular fundi should precede those showing pathological conditions. Slit lamp pictures of normal and abnormal crystalline lenses are also missing. At the end of each chapter a small number of references, mostly of papers written in French, is given. Although the American reader will hardly feel any need to consult this book, future additions and editions might turn it into a valuable contribution to ophthalmologic literature.

Medizin in Bewegung: Klinische Erkenntnisse und ärztliche Aufgabe. Von Richard Siebeck, D.Dr. med. Professor der inneren Medizin in Heidelberg. Second edition. Cloth. 33 marks. Pp. 493. Georg Thieme, Diemershaldenstrasse 47, (14a) Stuttgart O; (agents for U. S. A., Grune & Stratton, Inc., 381 Fourth Ave., New York 16), 1953.

"Medicine in Motion" is a record of Professor Siebeck's clinical experience covering more than three decades. Emphasis is placed on the thought that the patient is an individual and must be treated as such; no case history is ever completely identical with another history, and no clinical picture ever corresponds completely to the textbook description. The chapter entitled "Diseases and Personality" stresses the importance of the personality in patients with peptic ulcer. The sympathetic nervous system is discussed in connection with thyrotoxicosis and its treatment. There are chapters dealing with metabolism and various metabolic disorders, with acute and chronic infections, degenerative disease of the cardiovascular system, and arterial hypertension. A chapter entitled "Disease and Death" deals with cancer, particularly cancer of the stomach. While the psychosomatic approach and psychoanalysis are discussed particularly in connection with neurotic reactions, psychosomatic treatment is stressed throughout the work. The chapter on social pathogenesis discusses the role of the physician in social insurance, especially in social medicine and in occupational medicine. In this edition, revisions and improvements were made particularly in the chapters on infectious disease and on hypertension. The work contains a wealth of material that would prove valuable to the practitioner and internist with a good command of German.

Textbook of Obstetrics and Obstetric Nursing. By Mae M. Bookmiller, R.N., Assistant Professor of Clinical Nursing, New York University College of Medicine, New York, and George Loveridge Bowen, A.B., M.D., Clinical Professor of Obstetrics and Gynecology, New York University College of Medicine. With original drawings by Frank Netter, B.S., M.D. With section on newborn by Harry Bakwin, B.S., M.D., Professor of Clinical Pediatrics, New York University College of Medicine. Second edition. Cloth. $5.50. Pp. 768, with 346 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; W. B. Saunders Company, Ltd., 7 Grape St., Shaftesbury Ave., London, W.C.2, 1954.

This textbook, now in its second edition, is generally excellent. Its simplicity of presentation should make it most valuable to student nurses with too little time to study and absorb all of the scientific jargon of the highly technical world that engulfs them. The authors have succeeded in presenting their work at an educational level understandable to the high-school graduate and the girl with, at most, one or two years of college education. The text is most readable, profusely and beautifully illustrated, yet covers adequately the subject matter of the specialty.

QUERIES AND MINOR NOTES

SELF-MEDICATION FOR HYPERTENSION

TO THE EDITOR:—*In this community it is an established custom for patients to treat themselves for hypertension with small daily doses of magnesium sulfate, sometimes combined in equal parts with potassium bitartrate. Please discuss this medication.* *M.D., Georgia.*

ANSWER.—The community practice of self-treatment described in your question as an established local custom is dangerous. You stated that magnesium sulfate and potassium bitartrate are self-administered for hypertension. Although these agents in small daily doses are not particularly harmful, the practice of self-diagnosis and self-treatment for a condition as serious as hypertension is. With accurate diagnosis, continuous observation, and use of the medicaments and diet currently available, much can be done by the physician to alleviate hypertension and prevent or delay serious complications.

DISCOLORATION OF THE TONGUE

TO THE EDITOR:—*What is the significance of a brown, not black, tongue and also of one yellowish-tan in color? The yellowish-tan tongue I see in a large number of patients. It occurs on the central dorsal surface. The dark brown tongue, I have seen only about four times.*

H. Edward Hengen, M.D., Pattonville, Mo.

ANSWER.—A yellow to brown discoloration of the dorsum of the tongue is generally due to the staining of a previously coated tongue by certain foods, drugs, dyes, tobacco, or possibly chromogenic organisms. The type and intensity of the color depends on the staining agent and the duration of its use. Coating of the tongue results from a failure of the normal cleansing action of mastication and salivation to remove desquamated cells and other debris from the surface. Such factors as dehydration, gastrointestinal disease, and impaired mastication most frequently produce this condition. Brownish discoloration of the central third of the dorsum of the tongue is frequently associated with hypertrophy and matting of the filiform papillae. In addition to the factors already mentioned the following should also be considered: (1) the oral use of penicillin and other agents in troches and sodium perborate and (2) the systemic administration of antibiotics. There is apparently no direct relation between these conditions and nutritional disturbances. In some instances no specific cause is found. Further information is given in the chapter by Sarnat on "The Tongue in Health and Disease" in Portis' "Diseases of the Digestive System" (ed. 3, Philadelphia, Lea & Febiger, 1953).

RECTAL BURNING SENSATION AND CHLORTETRACYCLINE

TO THE EDITOR:—*What can be done to combat severe rectal burning following use of chlortetracycline (Aureomycin)?*

Henry A. Doorn, M.D., East Ann Arbor, Mich.

ANSWER.—To combat severe rectal burning following the use of chlortetracycline (Aureomycin), one should give 2 drachms (8 cc.) of elixir of Rubraton (containing vitamin B_{12}, folic acid, and ferric ammonium citrate) with each dose of the chlortetracycline. The elixir of Rubraton should be taken four times daily for one week after cessation of the chlortetracycline treatment.

If the rectal itching persists, the patient should be given a rectal suppository that contains 10 grains (0.6 gm.) of sodium alkyl sulfate, and enough cacao butter to make 3 gm. The patient should insert this into the rectum immediately after a bowel movement and before retiring at night. These measures should also control the itching around the anal region, associated with the use of oxytetracycline (Terramycin).

ODORS OF URINE AND STOOLS

TO THE EDITOR:—*What substances in the urine and stool impart the distinctive odors of each?* *M.D., New York.*

ANSWER.—The normal odor of stools arises from indole and skatole, which are derived from the deamination and decarboxylation of protein by putrefactive bacteria. The putrefactive process may also produce such substances as methyl mercaptan and hydrogen sulfide, which will add to the disagreeable odor of the feces. The offensive odor is particularly intense with a high protein diet or during the decomposition of blood or necrotic tissue within the bowel. A sour, rather rancid odor, occurs normally in infants and is due to fatty acids in the stool. The odor is also noticed in feces of adults or children with steatorrhea.

Normal freshly voided urine is almost odorless. The cause of its faintly aromatic smell is not definitely established. It has been attributed to volatile organic acid or to a substance named "urinod," the exact nature of which is unknown. On prolonged standing the urine acquires a "uriniferous" or ammoniacal smell due to ammonia formed during the decomposition of proteins and aminoacids in the urine. Urine with this odor may be passed when there is pronounced retention in the bladder or when large numbers of bacteria are present. Some articles in the diet may affect the odor of the urine. Of these, asparagus produces the most characteristic smell, which is due to methyl mercaptan. A fruity odor due to acetone bodies may be associated with the urine in diabetes, starvation, cyclical vomiting, and febrile states in children. Urinary infections may produce a putrid or a fishy smell, the latter being associated with the presence of coliform bacteria.

GLYCOL VAPORIZERS FOR DISINFECTING AIR

TO THE EDITOR:—*Can you give me any information regarding the efficacy of the Glycolator (a device to vaporize glycols) with trichlorethylene used as a preventive for upper respiratory infections?*

William C. Kinsey, M.D., Erie, Pa.

ANSWER.—It must first be pointed out that trichlorethylene is not the drug used in devices promoted for the prevention of upper respiratory infections. Trichlorethylene is a volatile analgesic agent. The use of triethylene glycol vapors for the control of bacteria in large spaces has been reported. Published studies have shown that the incidence of air-borne disease and cross infections can be reduced under experimental conditions. However, the presence of glycol vapor in a space controls spread of disease only within that space and confers no degree of immunity to a person exposed in other areas. Hence, the person may move from a protected area to another room where there is no protection and there be exposed to disease-causing organisms. In one study in which the efficacy of triethylene glycol vapor as an agent for sterilizing room air was tested, it was shown that, by the determination of the content of bacteria in the air and by observation of the absentee and weekly incidence rate for minor respiratory illness, under conditions of the experiment it was impossible to demonstrate any reduction in the number of air-borne bacteria, any reduction in the absentee rate, nor any reduction in the incidence of minor respiratory illnesses. The general application of glycol vaporizers for disinfecting air in homes, offices, schools, barracks, factories, or places of public congregation as a practical method of preventing the spread of upper respiratory disease cannot be recommended.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any official bodies unless specifically so stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

AFIBRINOGENEMIA

TO THE EDITOR:—*In a case of afibrinogenemia it was discovered that the mother was Rh-positive and the resulting child was Rh-negative. Is it possible that antigen from the mother could pass through the placental barrier causing antibody formation in the fetus's blood, which then returns to the mother's blood causing a breakdown of mother's blood cells and resulting in no clotting in the mother?*

Michael N. Lavacca, M.D., Bronx, N. Y.

ANSWER.—Evidence is available that indicates that the fetus in utero is incapable of forming antibodies. In fact, the newborn baby depends for his immunity on antibodies passively acquired from the mother by placental filtration. Therefore, this cannot be the explanation for afibrinogenemia in pregnancy. According to the most plausible explanation that has been suggested to date, afibrinogenemia is due to entry into the maternal circulation of thromboplastic material from the placental site. This problem was reviewed in an editorial in THE JOURNAL, Jan. 2, 1954, page 60.

EXCESSIVE FLOW OF TEARS

TO THE EDITOR:—*I have seen several persons in the age group from 40 to 65 who produced an excessive amount of tears. This has been associated with no infection or fungus involvement of the lacrimal apparatus. Irrigating and probing of the lacrimal apparatus is easily performed. There was no evidence of abnormal position of the lids, and the puncta appeared normal. Dilatation of the puncta has been of no benefit. I understand that Bruckner has advised the use of 5 drops of 2% dihydroergotamine, three times daily in these cases. I would appreciate further advice regarding this method of treatment.*

R. A. Donald, M.D., Fresno, Calif.

ANSWER.—Excessive flow of tears may be the result of stimulation of the fifth nerve endings, especially those ending in the cornea and conjunctiva. It can be caused reflexly by sneezing, coughing, vomiting, and finally, in man, by psychic stimulation. The psychic response can be checked by blocking the sphenopalatine ganglion. Tearing due to fifth nerve stimulation can be inhibited by surface anesthesia or by paralysis of the ophthalmic division of the fifth nerve. Psychic tearing is always bilateral and cannot be inhibited by surface anesthesia or by paralysis of the fifth nerve. The sympathetic nerve is said to control normal lacrimal secretion, while the facial is responsible for the occasional copious flow of weeping. Except in cases of weeping due to stimulation of the fifth nerve endings, instillation of drugs into the cul de sac is futile.

SPIDER-BURST TYPE OF VARICES

TO THE EDITOR:—*I would appreciate information on treatment of spider-web deformities of varicosities. This particular patient has had the veins stripped previously, but the small spider-web veins remain.* *M.D., North Carolina.*

ANSWER.—Treatment of superficial, cutaneous, spider-burst type of varices secondary to varicose veins is not necessarily indicated. However, for cosmetic purposes or because of pain due to engorgement occurring during the menses, treatment may consist of the needle injection of a sclerosing solution locally. Obliteration of these veins is accomplished by injecting bubbles made by vigorous shaking of a 5% solution of sodium morrhuate within a syringe before injection. A 26 gauge needle is used for entering the small venules, which must be done carefully because of the fine caliber of these vessels. The injected bubbles ascend into the ramifying tributaries. On withdrawal of the needle the region should be massaged in order to bring the venule walls into contact with the solution. Discoloration occurs but disappears with completion of the resolution after which the skin appears normal in color as adjacent areas. Some of the smaller vessels can be obliterated by electrolysis or the high frequency current. The electrolysis needle is inserted and withdrawn with the current on, in contrast to practice in removing hairs, where the current is on only while the needle is at the site of action.

OCULAR PROBLEMS OF ALBINOS

TO THE EDITOR:—*I would like information on care of the eyes of an albino, and also on the feasibility of using a telescopic lens for this patient, a 12-year-old boy trying to avoid use of sight-saving texts.*

L. W. Holland, M.D., Chamberlain, S. D.

This inquiry has been referred to two consultants, whose respective replies follow.—ED.

ANSWER.—There is no unanimity of opinion concerning the management of the ocular problem in albinos. Treatment for each patient should be carefully individualized. A thorough ophthalmologic examination is requisite, including study of the external structure and slit lamp, ophthalmoscopic and cycloplegic refraction examinations. Tinted lens are readily accepted by most patients with tints ranging from no. 2 to no. 4 Softlite. In specific cases telescopic lenses are used with gratifying success. The telescopic lenses are usually successful in direct proportion to the time the ophthalmologist is willing to spend in teaching the patient their use. Medical therapy (enzymic) has not been satisfactory, although the outlook for the future is promising.

ANSWER.—The eyes of an albino are so defective in pigment that central visual acuity is reduced, bright light annoys, and the eyeballs are in constant motion. The first essential in the maintenance of maximum efficiency is careful correction of the refraction error, which may be difficult because of the lateral nystagmus. The lenses should be dark, either black or one of a special type like the Crooksite or Softlite lenses. These will reduce the glare, lessen the photophobia, and afford much comfort. Telephoto lenses rarely improve the sight, and contact glasses are not indicated. Tattooing of the cornea is useless. If the vision with the best lenses is more than 20/100, a patient with normal mentality can keep up with regular class work and does not have to be in a special class. When he has less than 20/100 vision, sight-saving schools are preferable. So much depends on the individual and his adaptability and especially the interest of his teachers that no set rule applies to all. Many complete albinos are active in regular school life and even with 20/100 vision carry on close confining work.

PERCENTAGE OF DISABILITY

TO THE EDITOR:—*Is there any way to calibrate accurately the percentage of disability in a patient who has unilateral but recurrent nerve palsy secondary to injury?*

Walter T. Flakerty, M.D., Michigan City, Ind.

ANSWER.—The extent of disability of the body or any part of the body should be based on loss of function. According to McBride in his book "Disability Evaluation" (ed. 5, Philadelphia, J. B. Lippincott, 1953), 100% functional capacity may be divided into percentage values as follows: quickness of action, 10%; security and confidence, 10%; coordination, 20%; strength, 20%; endurance, 20%; added risk, 10%; and employability, 10%. To determine disability on your patient, consider the percentage loss of each of these seven functional factors, and the sum will be the percentage loss of functional disability.

SMALLPOX VACCINATION

TO THE EDITOR:—*I have vaccinated a baby four times for smallpox and each time I had "no take." The mother says she has never been able to have a successful vaccination, and the grandmother gives the same story. Is there such a thing as an inherited resistance to vaccinations for smallpox?*

Martin Karr, M.D., San Mateo, Calif.

ANSWER.—There is no such thing as a permanent inherited resistance to smallpox. The logical procedure is to revaccinate the child at periodical intervals of say six months unless there are contraindications to doing so.

ASTEREOGNOSIS

To the Editor:—*Would a daily dose of 50,000 to 100,000 units of vitamin A over a period of eight months cause astereognosis and onycholysis in a 50-year-old woman? Except for the astereognosis, the neurological examination discloses no abnormality, and there is no evidence of peripheral vascular disease. The patient has been studied from a dermatological and allergic standpoint without disclosure of an underlying cause for these changes.*

John D. German, M.D., Clintonville, Wis.

Answer.—Astereognosis has not been observed in hypervitaminosis A, even though, in two adults reported on the amount of vitamin A ingested was very large (600,000 units daily for 18 months in one case and 100,000 units daily for almost four years in the second). The pathological findings in experimental and clinical hypervitaminosis A do not suggest that astereognosis could be a related manifestation of this entity. Changes in the nails are noted concomitantly with skin changes in chronic vitamin A poisoning, the nails returning to normal much later than the skin. Softening, increased brittleness, and splitting of the nails have been observed, but onycholysis has not been reported.

References

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INDUSTRIAL BLINDNESS

To the Editor:—*In evaluating loss of visual efficiency in injured laborers in relation to our workmen's compensation law, we use the standard method approved by the House of Delegates of the American Medical Association, Atlantic City, N. J., May 26, 1925. In measuring the visual acuity for distance, we use the Snellen's test card for distance vision and for near vision the rating card prepared by the A. M. A. Section on Ophthalmology, which corresponds to the Snellen's notation for near vision. Our difficulty arises when the distance vision is less than 20/200 and the near vision less than 14/224, these corresponding to the largest letters printed on these cards. In the table "Percentage loss of visual efficiency corresponding to Snellen's notations for distant and for near vision for measurable range of quantitative visual acuity," under section 3 of the above-mentioned "Standard Method of Appraisal of Loss of Visual Efficiency," the smallest visual efficiency recorded is 20/800 for distance and 14/560 for near of 0.1% visual efficiency. We would like to know how to evaluate visual efficiency when the vision is less than 20/200 for distance and 14/224 for near.*

Jose S. Santillan, M.D., Manila, Philippines.

Answer.—The answer seems to be simple, since 20/200 for distance is regarded as industrial blindness by every state in the United States, and, since 14/140 is also industrial blindness, any industrial employee with visual acuity of less than 20/200 and 14/140 is regarded as industrially blind. Since the minimum visual requirement for industrial employees is 80%, any degree of visual acuity equal to this or below is regarded as industrial blindness, which entitles the worker to 100% compensation based on one eye and often a pension for life if both eyes are involved.

WEARING MASKS IN NURSERIES

To the Editor.—*Please discuss the rationale for the increasing tendency of hospital nurseries to abandon the practice of requiring masks to be worn.*

James W. Todd, M.D., Virginia Beach, Va.

Answer.—Those who have investigated this matter are of the opinion that the technique of using the mask has the most important bearing on its usefulness. If the mask is touched with the hands, it is worse than if none had been worn at all. It is most difficult to set up and maintain proper mask technique. Hence, there has been a tendency for many hospital nurseries to abandon the practice of requiring them.

ELECTRIC SHOCK

To the Editor:—*A 53-year-old man previously in good health accidentally received a shock from 220 volts of electricity, which "froze" him to the wire but did not cause loss of consciousness. Having no symptoms directly referable to the heart, he continued working for five and one-half weeks and then died suddenly, presumably of acute coronary thrombosis. Could there be any relation of the latter to the electric shock?*

M.D., Missouri.

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—It seems quite impossible that the electric shock was involved in the death of this patient, even assuming that he died of an acute coronary thrombosis. Cardiac death following electric shock is due to ventricular fibrillation, but this event is coincidental with the shock and death follows almost immediately. It is possible for 220 volts to produce this result if the heart is directly in the track of the electric current. Ventricular fibrillation is a disturbance of rhythm that does not necessarily involve damage to the heart. It is generally conceded that, if the heart escapes this disturbance in rhythm in cases of electric shock, there is no evidence of cardiac damage. No textbook on heart disease mentions electric shock as a predisposing cause of coronary occlusion. The following quotation is from Johnstone's "Occupational Diseases" (Philadelphia, W. B. Saunders Company, 1941): "It should be reiterated that although ventricular fibrillation is the common cause of immediate death [in electric shock] there exists no evidence that permanent damage exists in the heart of one who has recovered from electrical injury." Unheralded acute coronary thrombosis in a 53-year-old man is a rather common occurrence, and, if that is what happened to this patient, it was entirely unrelated to the electrical injury of five and one-half weeks earlier.

Answer.—It is unlikely that there is any relationship between the electric shock that this man had and his death from heart failure five and one-half weeks later. The only circumstance in which death due to electricity is not almost immediate is when it results from the complications of severe external burns. Death from electric shock is due to heart failure or to paralysis of the respiratory centers, and in either circumstance the functional failure occurs while the electric current is passing through the body. If the shock is followed by sufficient restoration of cardiac and respiratory functions to permit the victim to return to work, there would be no reason to believe that it had caused any permanent internal injury.

Reference

Moritz: Physical Agents in Injury and Disease in Pathology, Anderson, editor, St. Louis, C. V. Mosby Co., 1953, p. 138.

URINARY AND FECAL INCONTINENCE

To the Editor:—*A woman, aged 65 years, has been hypertensive for 20 years. She has been free of any renal, optic, or cardiac abnormality. Six weeks ago she suffered a coronary attack and three days later a complete left hemiplegia. There has been constant urinary and fecal incontinence, and I would like to know what to do for this. There has been very slight return of function in the left hand but none in the lower extremity in spite of physiotherapy. The blood pressure is still 220/130 mm. Hg.*

M.D., Pennsylvania.

Answer.—Urinary and fecal incontinence is not a usual concomitant of hemiplegia. The likelihood of more extensive cerebral infarction than occurs generally with hemiplegia should be considered. Presumably the patient is aware of her surroundings. The insertion of an indwelling catheter provides a convenient method of caring for such a patient's urinary requirements. The catheter should be changed about every 10 days, and infection controlled by the oral administration of a sulfonamide, such as sulfisoxazole (Gantrisin), 0.5 gm. three times daily. The usual precautions of sulfonamide therapy should be observed. Usually the bowels can be attended to by giving an enema every one to three days. A low residue to normal diet would be proper. Physical therapy should be continued.

INGUINAL LYMPHADENOPATHY

To the Editor:—*A man has had right inguinal lymphadenopathy for one year. He recalls no initial genital lesion. Nine months ago, the largest lymph node was incised and he was given penicillin with no apparent benefit, although a few days later the node suppurated and drained. Eight months ago, when he came under my care, both Frei and Ducrey antigen tests were negative and there was a large (6 by 5 cm.) firm, matted, fixed, tender node in the lower right inguinal area extending into the right femoral triangle. The inflammation responded to chlortetracycline (Aureomycin), and after six weeks the mass was barely palpable except for a firm area beneath the incision scar. Four months ago the same matted node became inflamed and swollen again while the patient was being self-treated with 50 chlortetracycline capsules (250 mg.). Recently a repeat Frei test was positive. Other discrete nodes are enlarged and inflamed in both inguinal groups. Thorough trials on triple sulfonamides, oxytetracycline (Terramycin), and chloramphenicol (Chloromycetin) have given no response except to reduce the acute inflammation. What could be expected from surgical incision or excision? Would direct injection of the nodes with chlortetracycline be beneficial? Small areas of the large node intermittently have been soft, but attempts at aspiration have failed to yield any pus.*

Richard H. Mott Jr., M.D., Auburndale, Fla.

Answer.—The diagnostic situation in this patient cannot be solved without biopsy and surgical pathological examination of one or more of the involved nodes. It is suggested that the originally involved node in the lower right inguinal area and one of the other "discrete nodes" be excised for pathological examination. A number of diagnostic possibilities suggest themselves, among them lymphogranuloma venereum, cat scratch disease, tuberculosis, or a lymphoblastoma. Lymphogranuloma venereum seems relatively unlikely since the Frei test was negative four months after the onset. The recent positive Frei test does not necessarily make the diagnosis. What antigen was employed in performance of the Frei test? It is probably desirable to repeat this with a pure virus antigen (Lygranum). Are there enlarged nodes elsewhere; and especially does the patient have any radiological evidence of mediastinal nodes?

HEPATITIS

To the Editor:—*Infectious hepatitis developed in a patient on Jan. 20, 1954. His icterus cleared up two weeks after the onset. At present his urine is free of bile; however, his blood shows bilirubin 1.5 mg. per 100 cc. Please state when the patient will be safe and capable to resume work. He has gained 10 lb. (4.5 kg.); he is 30 years old, 6 ft. (183 cm.) tall, and weighs 182 lb. (82.6 kg.). Before he got sick, he weighed 175 lb. (79.4 kg.).* *D. J. Louis, M.D., Chicago.*

Answer.—Another quantitative van den Bergh test, cephalin flocculation determination, and, if the bilirubin is not elevated, a sulfobromophthalein (Bromsulphalein) excretion study should be done. The latter is probably the most sensitive of all the tests for hepatic injury. If it is normal, there probably is no reason to worry about the patient's condition. If, on the other hand, the bilirubin is not clearly normal and the sulfobromophthalein retention in the blood is still elevated, the patient should rest two or three weeks longer.

THYROTOXICOSIS IN A CHILD

To the Editor:—*A diagnosis of thyrotoxicosis in a 7-year-old girl has been made clinically and confirmed by laboratory procedures. What is the latest opinion regarding medical treatment as compared with surgical therapy?*

Ronald O. Germain, M.D., El Paso, Texas.

Answer.—Assuming that there is no question of the diagnosis of hyperthyroidism, treatment for a 7-year-old girl is a matter of individual choice. In general in hyperthyroidism in children, which is almost always of the toxic diffuse goiter (Graves' disease) type, antithyroid drugs do not effect permanent cure and should not be given indefinitely over prolonged periods of time. The basic choice lies between preparation with one of the antithyroid drugs followed by thyroidectomy and the use of radioactive iodine. There is a strong objection in some parts of the country to the use of radioactive iodine in children of this age for fear that the irradiation to which the thyroid is subjected might later in life prove to be carcinogenic. There is as yet no clinical evidence to substantiate this point of view, but it is a consideration that must be carefully weighed. One would certainly be unwilling to subject a patient of this age to extensive irradiation, and if complete control of the hyperthyroidism could not be obtained with 10 or at most 15 mc. of radioactive iodine one would be tempted to abandon irradiation and resort to thyroidectomy. Everything considered, if the child is a good surgical risk and responds well to preparation with an antithyroid drug and iodine, surgery would probably be simplest.

FIBERGLAS

To the Editor:—*Is there any danger working in an atmosphere filled with filings from Fiberglas, without the use of a mask or dust filter? Does inhalation of Fiberglas filings or dust cause pneumoconiosis?* *M.D., Pennsylvania.*

Answer.—Fiberglas dust will not produce any pneumoconiosis that is analogous to silicosis. On a mechanical basis Fiberglas dust, or more precisely spicules, may irritate eyes, mucous membranes, but chiefly the damage is to the skin. Presently much Fiberglas is utilized in plastic lamination products. Many of the plastics in unpolymerized form are distinct skin irritants or sensitizers. The combination of a mechanical irritant plus the chemical irritant in the form of the plastic may lead to dermatitis. Whenever the dust concentration from Fiberglas is high, mechanical exhaustion is desirable. In hot seasons or in hot workrooms sweating facilitates the skin damage so that air conditioning has its advantages. Some silicone barrier creams, and a few barrier creams without a silicone content, substantially protect the skin surface. As a rule, the coarser the glass fiber is the greater the prospect of injury.

PULMONARY EMBOLISM

To the Editor:—*Please advise me as to the incidence of pulmonary embolism following major surgical procedures. Do you know the incidence of pulmonary embolism following saphenous vein ligation? Is the incidence greater when stripping of the saphenous vein is done?*

John P. Gifford, M.D., Vero Beach, Fla.

Answer.—The incidence of pulmonary embolism following major surgical procedures varies between 0.5 to 8%; length of operation, blood loss, hypotension, hemoconcentration, previous thromboembolism, and carcinomatosis are some of the factors that contribute to an increase in incidence. After ligation of the saphenous vein the incidence is about 1:2,000. No data are available regarding the incidence of pulmonary embolism after stripping of the saphenous vein.

COMMINUTED COMPOUND FRACTURE

To the Editor:—*In a severely comminuted compound fracture caused by a high power rifle bullet, what is the soonest that an intramedular nail may be inserted? Is there danger of osteomyelitis if the pinning is done before the wound has had a good chance to heal?* *M.D., Arizona.*

Answer.—If the severely comminuted compound fracture is treated adequately within a period of less than eight hours after injury, so that the wound is carefully cleaned and débrided, it would be good practice to proceed at that same time to insert the intramedullary rod and subsequently, during the same operation, to close the wound. If necessary, relaxing incisions at a distance from the entrance or exit of the bullet should be made to release the tension so that the skin can be closed. The danger of osteomyelitis is present only if the bullet wound is not promptly and adequately treated, the wound remains open, and suppuration occurs within the wound. In that event the introduction of an intramedullary pin should not be undertaken until the infection is completely cleared up and the primary wound has been healed for a period of three or four weeks.

THRUSH

To the Editor:—*A boy, aged 7, has had severe resistant oral thrush since age 2. Gentian violet, locally, benzalkonium (Zephiran) chloride solution, locally, and high doses of ascorbic acid and vitamin B complex have resulted in only slight improvement. Saturated potassium iodide solution in doses up to 20 minims three times daily resulted in definite improvement but was discontinued because of the untoward symptoms that followed. Are there any further therapeutic possibilities? Have stilbamidine or diiodohydroxyquinoline (Diodoquin) for oral administration been used in this condition?*

M.D., Montana.

Answer.—It is assumed that the condition present in this patient's mouth has been demonstrated to be thrush by the usual bacteriological procedures. The long duration of this disease brings up for consideration whether this is really a case of thrush. It would have been helpful to know whether the usual bacteriological procedures have been employed to establish the diagnosis. The therapeutic agents usually effective in the treatment of thrush have already been employed. There are no known clinical reports concerning the use of stilbamidine or diiodohydroxyquinoline given orally for the treatment of thrush. Sodium caprylate is a very active fungicide. A 10% aqueous solution can be applied topically twice a day to the lesions. If improvement does not occur, a review of the diagnosis is in order.

DEXTROSE IN DISTILLED WATER PRECEDING TRANSFUSIONS

To the Editor:—*At our hospital, hundreds of blood transfusions have been preceded by administration of 5% dextrose in distilled water. Although agglutination or rouleaux formation is seen in the tubing when the blood is started, no reactions due to this have been seen. Some of the surgeons look with horror at the clumping and claim that deaths have resulted, although none are able to quote anything from the literature or state any authentic case. Is there any harm in preceding a blood transfusion with 5% dextrose in distilled water?*

M.D., Washington, D. C.

Answer.—It is inadvisable to administer dextrose solutions with citrated whole blood. De Gowin, Harden and Alsever (Blood Transfusion, Philadelphia, W. B. Saunders Company, 1949, p. 278) have called attention to the danger of extravascular hemolysis resulting from the mixture of stored blood and dextrose solutions. The agglutination that occurs in a mixture of dextrose solution and citrated whole blood is reversible; nevertheless, Wilson (*Am. J. Clin. Path.* **20**:667, 1950) has reported a transfusion reaction traceable to this phenomenon. Dreyfus and Salmon (*Presse méd.* **60**:845, 1952) have also pointed out the danger of agglutination and of increased fragility of red cells exposed to dextrose solutions. They have presented results of in vitro and in vivo studies to support their conclusion that the practice of giving simultaneous infusions of dextrose solutions and whole blood should be abandoned.

PANCREATIC CYST

To the Editor:—*Six months ago I did a marsupialization on a post-traumatic pseudopancreatic cyst and have been packing it weekly ever since. At first the cyst seemed to fill in rather rapidly, but then its filling became stationary and, to all appearances, may remain forever at its present size. Can you suggest a method for making this fill in more rapidly? So far I have been packing it with iodoform gauze only.*

M.D., Arizona.

Answer.—The cyst can be outlined by injecting iodized oil (Lipiodol) and taking a roentgenogram. If there is no change in size within another one or two months, an effort should be made to solve the problem of drainage and to prevent a recurrence of the cyst if the external opening closes. The safest and simplest method is to provide internal drainage of the cyst. A Roux Y-formed anastomosis of the jejunum to the cyst wall can usually be done without difficulty, passing the limb of the Y through the transverse mesocolon or passing it in front of the colon, depending on the local situation. Absorbable surgical sutures with a 1½ in. (3.8 cm.) anastomotic opening will suffice. It is possible to anastomose the stomach to the cyst, but the Roux Y-formed is safer.

BCG VACCINE

To the Editor:—*Is it advisable to use BCG vaccine to raise immunity against tuberculosis in a young adult who has a negative skin test? He has had a negative chest roentgenogram and is in apparently normal health but is very tall and thin. What preparations are advisable, and where are they obtained?*

M.D., Pennsylvania.

Answer.—The question of advisability in use of BCG vaccine is dependent altogether on the circumstances. If the person is an ordinary citizen and is going about his way of life without any unusual contacts with tuberculosis, BCG vaccine is not necessary, although it would do no particular harm. If the person has negative tuberculin and has tuberculosis contacts, such as cases of tuberculosis within the family circle, immediate or remote, or any work or association that brings him into immediate contact with tuberculosis patients, BCG vaccine would be recommended. There are several institutions in the United States that are preparing BCG vaccine at the present time. Tice Laboratory at the University of Illinois in Chicago and the laboratories at the Henry Phipps Institute in Philadelphia are two that would be satisfactory.

NARCOSYNTHESIS

To the Editor:—*I would like information on the use of small doses of thiopental (Pentothal) sodium intravenously in the treatment of psychoneurosis.*

A. C. Scott, M.D., Evansville, Ill.

Answer.—One of the therapeutic techniques developed to a large extent during World War II for acute war neuroses was narcosynthesis, utilizing sedation by amobarbital (Amytal) sodium or thiopental sodium given intravenously. A state of drowsiness, with relative freedom of inhibition, was created, resulting in a discharge of emotional experiences through talking without restraint. An attempt was made at the same time to reintegrate the patient's emotions into his traumatized personality. In the hands of Grinker and Spiegel (War Neuroses, Philadelphia, Blakiston Company, 1945) the results were excellent and a large percentage of the soldiers with acute cases were returned to duty. Patients with anxiety states, phobias, and some types of depression responded best; cases of hypochondria and excessive fatigue were more difficult to rehabilitate. The method of amobarbital sodium narcosynthesis, useful in acute war cases, with violent and explosive onset, has not been found so efficient in the case of peace-time patients with psychoneurotic symptoms. Other techniques have been used to greater advantage, but narcosynthesis still has a place, although not a very important one, in civilian practice. If the neurosis is rooted in trauma, with severe anxiety as the predominant symptom, narcosynthesis may elicit psychiatric material that resistance holds below the surface, but narcosynthesis is a somewhat hazardous procedure and should be used only by experts. Most psychiatrists favor the most regular and standardized forms of psychotherapy.

CATARACTS

To the Editor:—*What is the best and safest medicine to dilate the pupils of patients who have obstructive central cataracts? The desire is to dilate the pupil once daily for a short period to permit some reading.*

W. O. Bailey, M.D., Leesburg, Va.

Answer.—Generally speaking, if a cataract has progressed to a state where reading is no longer possible, the treatment of choice is surgical removal. A number of sympathomimetic drugs, such as phenylephrine (Neo-Synephrine) hydrochloride, hydroxyamphetamine (Paradrine) hydrobromide, epinephrine (Adrenalin), cocaine, and eucatropine, may be used for dilation if glaucoma is not present. If this is to be done daily, the patient must be definitely shown not to have glaucoma, with intraocular pressure measured before and after dilation by means of a tonometer.

DENDRITIC KERATITIS

To the Editor:—*What is the incidence of blindness as a sequel of the virus infection of the cornea, dendritic keratitis? What is the best treatment, and how may recurrences be prevented? I would like your opinion concerning the ingestion of raw onions as a therapeutic agent, containing a bactericide and antiviral agent. If bactericidal or antiviral compounds were absorbed from the digestive tract after the ingestion of onions and transferred by the blood stream to diseased organs, how could it be transferred to an avascular tissue, such as cornea?*

M.D., New Jersey.

Answer.—Blindness virtually never follows dendritic keratitis, although the inflammation may cause such marked scarring that vision is markedly reduced. In an editorial Thygeson (*Am. J. Ophth.* **36**:269, 1953) states that this is the most important specific keratitis in the United States. Prior to World War II he had observed only one case of bilateral dendritic keratitis in 14 years. During the war he saw several, and recently he observed three in one week. It is his impression that the disease has increased suddenly in severity and frequency. Furthermore there seems to be a higher incidence of associated lesions, such as disciform keratitis and uveitis. He also observed an extraordinary increase in the number of cases of primary ocular herpes, in which severe conjunctivitis with preauricular adenopathy resembled the changes seen in epidemic keratoconjunctivitis. Prior to the advent of cortisone, corneal perforation was an unheard-of complication in herpes corneae, and hypopyon was exceedingly rare. He has now seen two cortisone-treated patients with a hypopyon and has heard of three with corneal perforation.

The avascular cornea receives its nutrition from blood vessels at the limbus and possibly from oxygen from the atmosphere. Frequently the transfer of drugs from the blood stream to the normal cornea is not very marked, but in inflammation there is an increased blood supply with neovascularization of the cornea. Usually drugs are transferred to the tissue very rapidly under these conditions. Medically there seems to be no contraindication to the ingestion of raw onions, although social ostracism may be a high price for this empiricism. Effort should be made to interrupt the various trigger mechanisms, which in many cases occur with recurrences. The use of antibiotics and antihistaminics is worthy of trial when fever is the precipitating cause or when other such activating mechanisms as sunburn, menstruation, emotional crises, and allergy are known to be concerned.

STERILIZATION FOLLOWING MASTECTOMY FOR CANCER

To the Editor:—*A 32-year-old woman had a radical breast amputation two weeks after she noticed a lump in her breast. Thirty-two axillary lymph glands were examined, and one showed spread of the carcinoma. Histologically this was an adenocarcinoma. Is sterilization indicated, and if so should it be done surgically or by x-ray therapy?*

Fritz Koenig, M.D., Catlin, Ill.

Answer.—Sterilization is certainly indicated in this case and should be surgical. Oophorectomy has definite advantages over sterilization by x-ray. The surgical method is certain and permanent and removes ovarian function abruptly.

CHLOASMA

To the Editor:—*I have two patients with chloasma uterinum. These women are 26 and 28 years old. The lesions are very persistent and are distributed on the face, cheeks, and breasts. I would appreciate advice regarding treatment. Their ovarian cycles are normal.*

Ruben Gandelmann, M.D., Rio de Janeiro.

Answer.—The application to the patches of monobenzylether of hydroquinone often lightens the pigmentation of chloasma. A purified form marketed under the name of Benoquin is available. It must be used with caution, for it may irritate the skin if used too often or too freely.

PUFFY EYELIDS

To the Editor:—*What is the most frequent cause of puffiness of the upper eyelids? The patient lies on his right side mostly, and I wonder if this has anything to do with the fact that the right lids are a little more puffy than the left lids? Occasionally there is puffiness under the lower lids.*

E. L. Carenee, M.D., Champaign, Ill.

Answer.—The skin of the eyelids is very delicate and is only loosely attached to the underlying structures. Consequently, very small amounts of subcutaneous edema can cause considerable puffiness of the eyelids. The loss of elasticity of the lids with advancing age contributes to the condition. Mild noninflammatory edema of the eyelids without other ocular signs may have no significance in elderly people. It is commonly observed on the dependent side on arising from sleep. Edema of the lids of both eyes in the early morning is, however, suggestive of a disturbance in the systemic circulation. A complete general examination is indicated.

DISCHARGING EARS

To the Editor:—*I was interested in the query in* The Journal, *April 3, 1954, page 1236, about discharging ears. Congratulations on the answer to the question. For the first time, I have seen this direct advice given to such an inquiry: "All discharging ears call for a thorough investigation and treatment of the nose, sinuses, and nasopharynx as possible reinfecting sources." I have heard specialists in the treatment of ear, nose, and throat give long addresses on chronic purulent otitis media and never mention chronic sinusitis as an etiological factor. I had my baptism of fire in the terrible influenza epidemic of 1918, in which I was performing mastoid operations every day for some time. I soon noticed that these infections were also associated with a purulent sinusitis, practically always on the same side as the mastoid infection. Step by step, I followed this up and found that a certain percentage of the mastoid infections would not heal after operation. In these cases, I asked the patients to submit to a sinus operation, and in every one who submitted to the operation the mastoid infection cleared in a few days. The drainage stopped immediately and the healing was prompt and permanent. Since then, I have seen many cases of chronic purulent otitis media associated with a chronic purulent sinusitis. Every patient who submitted to an operation had stoppage of discharge from the ear immediately, and a new drum and hearing followed in a short time.*

In my judgment, any patient with chronic purulent otitis media should have his sinuses investigated as the first step. The ear is not the point at which to start investigation. I am firmly convinced that, in these cases, the eustachian tube acts as a sewer and drains the pus from the sinuses into the middle ear, where it causes a chronic abscess. Well-known otologists have wondered why a case of chronic purulent otitis media should start with a foul odor. The odor is not from the structures of the ear, but from pus from the sinus.

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To the Editor:—*I note in* The Journal, *April 3, page 1236, the comment on the use of powdered chlorophyll to combat the odor of discharging ears. While no one would disagree with the emphasis on the paramount importance of proper otoscopic interpretation of the underlying cause, I question the summary dismissal of chlorophyll-containing medications for deodorization of the discharge. As far as I know, 100% powdered chlorophyll would not be a feasible dosage form. I am currently using as a lavage in otitis media a solution made from a sodium propionate-chlorophyllin powder with considerable success. Here, again, the chlorophyll derivatives may be presumed to contribute to the cleansing and deodorizing effectiveness of the irrigation.*

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